EXPLORATION AND DEVELOPMENT OF BENZIMIDAZOLE-BASED PHOSPHINE LIGANDS TOWARDS SUZUKI-MIYAURA CROSS-COUPLING

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Exploration And Development Of Benzimidazole-Based Phosphine Ligands Towards Suzuki-Miyaura Cross-Coupling

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in partial fulfillment of the requirements

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Certificate of originality

I hereby declare that this thesis is my own research work carried out since my registration at the Hong Kong Polytechnic University for the degree of Master of Philosophy in September, 2008, and that, to the best of my knowledge and belief, it reproduces no material previously published or neither written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

YEUNG CHUNG CHIU

July, 2010

Abstract

"Exploration and development of benzimidazole-based phosphine ligands towards Suzuki-Miyaura cross-coupling"

Submitted by YEUNG CHUNG CHIU

For the degree of Master of Philosophy

At The Hong Kong Polytechnic University in August, 2010

The research study is focused on the development of easily accessible heterocyclic phosphine ligands. The first part of the investigation is the attempted study of electronic effects towards the reactivity of indolyl phosphine ligands while the second part is the design and synthesis of newly developed benzimidazole-based phosphine ligands and their applications on Suzuki-Miyaura Coupling.

In the study of indolyl phosphine ligand, we tried to examine the electronic effect by the incorporation of different substituted groups on the 5-position of the indole ring on the ligand template. We aim to study the importance of the electronic density on the phosphorus atom over the reactivity of the ligands. We propose that the reactivity of the ligands should be directly proportional to the electron density of P donor atom of ligands. A family of 5-substituted indolyl phosphine ligands were successfully prepared and their reactivity was compared by the same Suzuki coupling reaction under mild reaction conditions in order to demonstrate their reactivity differences. We

believe this research findings will contribute to the future development of related ligands.

In my second project, a new scaffold, benzimidazole, was used for the ligand design. Benzimidazole is attractive as it is commercially available with a reasonable price. In addition, the synthesis of benzimidazole-based phosphine ligand is atom economic that less side products are formed. However, using ligands with benzimidazole scaffold is not electron-rich enough for Suzuki coupling. Based on the research concept of my first project, we modified the ligand design by adding two methyl groups on the benzimidazole scaffold. The new dimethyl benzimidazole-based phosphine ligand is highly effective for Suzuki coupling of both activated and deactivated aryl chlorides with moderate catalytst loading.

Publications

1. So, C. M.; Yeung, C. C.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem*. **2008,** *73*, 7803-7806.

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YEUNG CHUNG CHIU

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Table of contents

Abbreviation

Ac	acetyl
Ad	adamantyl
Ar	aryl
Bn	benzyl
Bu or *n*Bu	(primary) butyl
Bz	benzoyl
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
Dppe	1,1'-bis-(diphenylphosphino)ethane
Dppp	1,1'-bis-(diphenylphosphino)propane
Dppb	1,1'-bis-(diphenylphosphino)butane
Dppf	1,1'-bis-(diphenylphosphino)ferrocene
DMF	dimethyl formamide
E+	electrophile
eq.	equivalent
Fur	furyl
GC	gas chromatography
h	hour
HPLC	high-performance liquid chromatography
HPMS	high-resolution mass spectrometry
*i*Bu	isobutyl
*i*Pr	isopropyl
J	coupling constant (in Hertz)
LDA	lithium diisopropylamide
[M]+	transition-metal pre-catalyst
Me	methyl
min	minute
MS	mass spectrometry
Ms	mesyl, methanesulfonyl
m/z	mass-to-charge ratio (in mass spectrometry)
Naph	naphthyl
NBD	norbornadiene
NMR	nuclear magnetic resonance

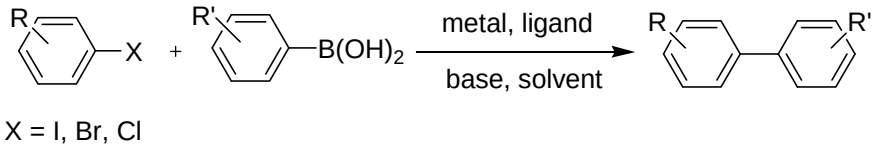
Nu-	nucleophile
Ph	phenyl
Pr	propyl
PS-DES	polystyrene-diethylsilyl
PS-Et	polystyrene-ethyl
PTC	phase transfer catalyst
py	pyridine
RT	room temperature
*s*Bu	secondary butyl
*t*Bu	tertiary butyl
THF	tetrahydrofuran
Tol	toluene
Ts	tosyl, toluenesulfonyl
Xyl	xylene
$[\alpha]_{D20}$	special optical rotation
σ_p	Hammett substituent constant
E_{TN}	normalized $E_T(30)$ solvent polarity

Chapter 1

Introduction

1.1 Suzuki coupling reaction

The last several decades have seen growing attention placed on the synthesis of compounds containing heterobiaryl moieties, which are commonly found in polymers,[1] ligands,[2] pharmaceuticals,[3] and functional materials.[4] Among the reported synthetic pathways, the palladium catalyzed Suzuki–Miyaura cross-coupling reaction between heteroaryl halides and arylboronic acids provides a general and applicable method for the preparation of heterobiaryl compound.[5] The Suzuki reaction, discovered by Akira Suzuki in 1979,[6] of aryl and vinyl halides or triflates with boronic acids has drawn a great attention because of its commercial availability of boronic acids.[7] They are nontoxic and stable to heat, air and moisture. And less side products are formed after the catalysis. The desired products are easily purified by column chromatography.



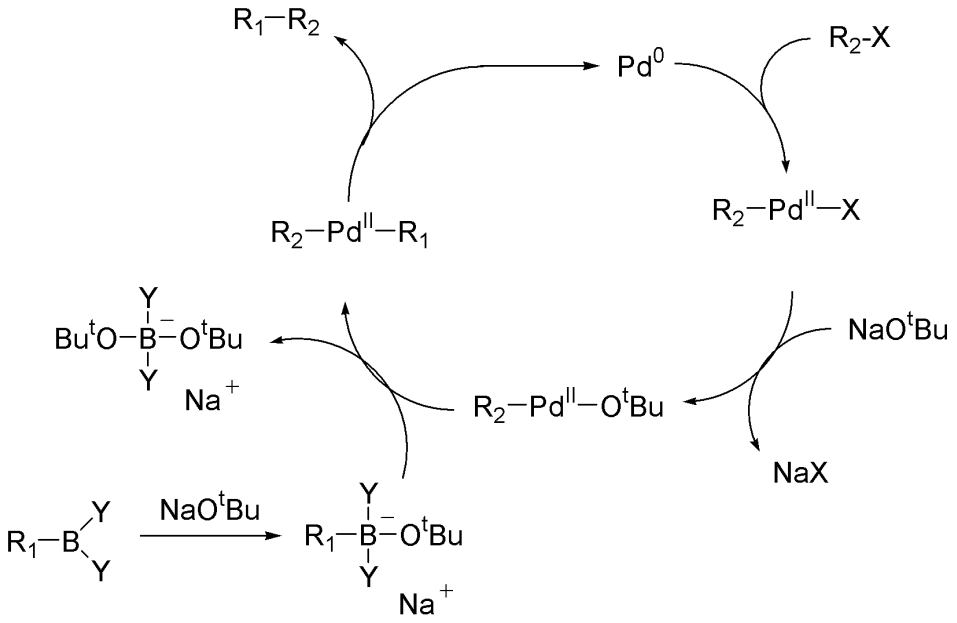
(Scheme 1: General equation for Suzuki coupling)

Among the aryl halides, aryl chlorides are the most preferable substrates because of their low cost and the wide diversity of available compounds.[8] However, a major limitation is that the bond dissociation energies for C-Cl bond is the second highest

among the other carbon-halide bond, resulting in poor reactivity of aryl chlorides.[9]

1.1.1. Suzuki coupling mechanism

The proposed mechanism of the Suzuki reaction is a three-step process. (Figure 1)



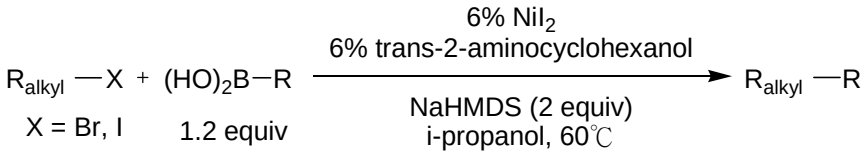
(Figure 1: The mechanism of the Suzuki reaction)

The first step is the oxidative addition in which the aryl halide is added to the palladium (0) metal and Pd is oxidized into Pd^{2+}.Secondly, during transmetallation,[10] the organic group attached to the boron atom become a more potent nucleophile by reacting with hydroxide ion from base, followed by a substitution reaction. The role of base is to facilitate the slow transmetallation of the boronic acid by forming a more reactive boronate species that can interact with the Pd metal center. The organic group attached to boron is transferred to the Pd^{2+} ion and replaces the halide ion. Finally, the complex undergoes reductive elimination to produce the desired bi-aryl product and regenerate the original palladium (0) catalyst.

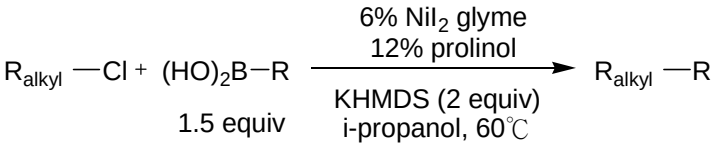
1.2. Metal for Suzuki coupling

1.2.1. Nickel-catalyzed Suzuki coupling

In 2006, Fu reported the use of amino alcohols as ligands for Nickel-Catalyzed Suzuki reaction of unactivated alkyl halides with aryl boronic acids.[11] The alkyl halides included secondary bromides, secondary iodides and primary iodides. The general equations are shown as follow:



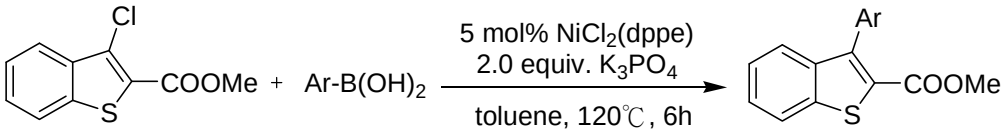
(Scheme 2: Nickel-catalyzed Suzuki coupling of aryl bromide and aryl iodide)



(Scheme 3: Nickel-catalyzed Suzuki coupling of aryl chloride)

The nickel-catalyzed reaction offered a few advantages that after the catalysis, the desired product was easily separated from the catalyst mixture. In addition, the nickel complex is air stable, less costly and easy to prepare for catalyst. The above properties are important when considering the scale-up of the reaction.[12]

Apart from Fu, Miura has also reported the nickel-catalyzed Suzuki-Miyaura cross-coupling for the first arylation of 3-chloro-2-methoxycarbonly benzo[b]thiophene in 2009 (Scheme 4).[13]

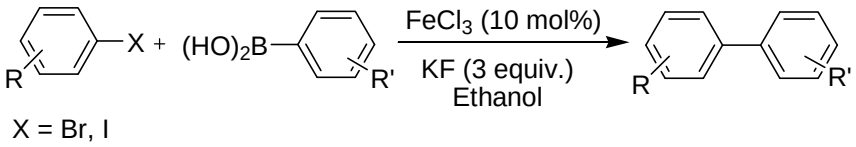


(Scheme 4: Nickel-catalyzed Suzuki coupling of 3-chloro-2-methoxycarbonly benzo[b]thiophene)

The nickel-based method has effective activation of C-Cl bond, resulting in the coupling of benzothiophene with phenylboronic acid in the presence of 5 mol% $NiCl_2$(dppe) and 2.0 equivalents of K_3PO_4 in boiling toluene. The product was further applied to the palladium-catalyzed decarboxylative arylation.

1.2.2. Iron-catalyzed Suzuki coupling

In 2009, Darcel reported a cross-coupling reaction of halogenoaryl compounds (X = I, Br) with aryl boronic acid in ethanol with catalytic amount of $FeCl_3$ and stoichiometric amount of KF (Scheme 5).[14]



(Scheme 5: Iron-catalyzed Suzuki coupling of aryl bromide and aryl iodide)

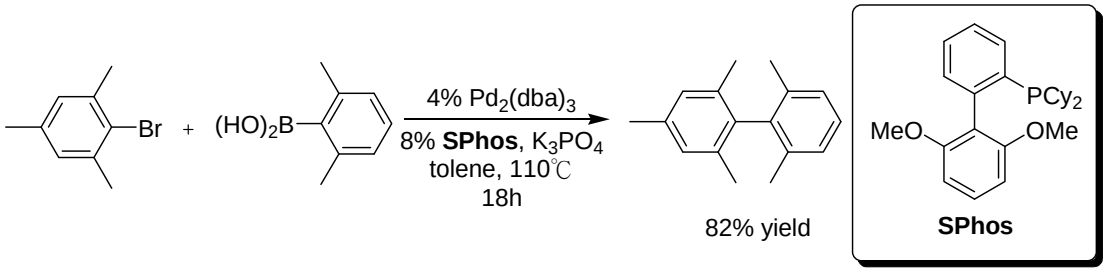
Many catalysts are formed by heavy or rare metals and their toxicity and expensive prices are the major concerns for large-scale industrial production. Iron is one of the most abundant metals on the earth and it is inexpensive and environmental friendly.

1.2.3. Palladium-catalyzed Suzuki coupling

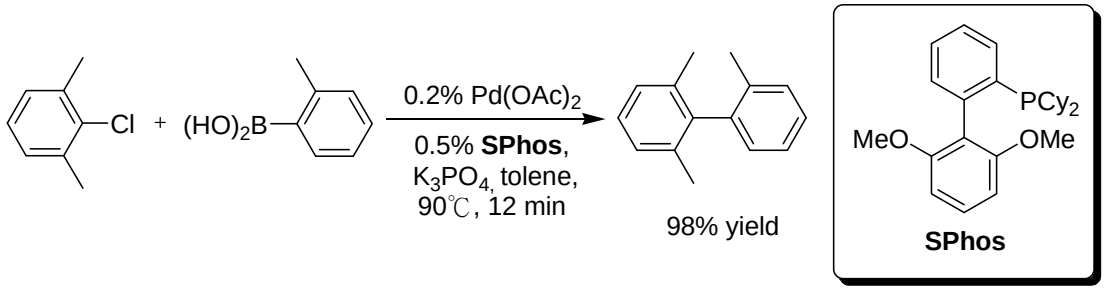
Palladium-catalyzed cross-coupling is versatile and highly effective for reactions like amination,[15] Heck reaction,[16] Hiyama coupling[17] and Suzuki coupling. However, there

are several disadvantages of using palladium catalyst system, such as high cost, toxicity and the potential contamination of the products.[18] The applications are limited in the massive large-scale industrial production, especially in the pharmaceutical industry which have to closely monitor the metal contamination of products. Despite the disadvantages, the effectiveness, efficiency and wide substrates availability outweigh the disadvantages of using palladium for catalytic reaction.

There are countless journals about the palladium-catalyzed Suzuki coupling. Aryl iodides,[19] bromides,[20] triflates[21] and chlorides are commonly used for electrophilic partners. In 2004, Buchwald and co-workers reported SPhos for the palladium-catalyzed Suzuki coupling of sterically hindered aryl bromides and aryl chlorides (Scheme 6 and 7).[22]



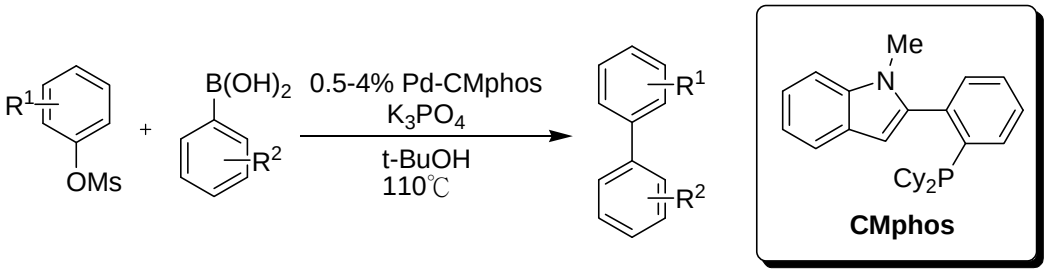
(Scheme 6: Palladium-catalyzed Suzuki coupling of aryl bromides using SPhos)



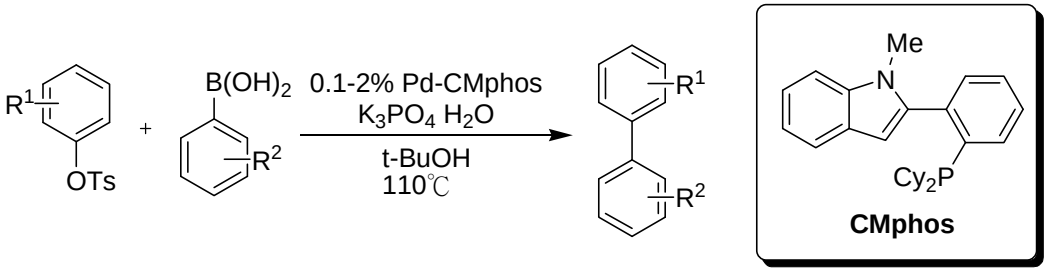
(Scheme 7: Palladium-catalyzed Suzuki coupling of aryl chloride using SPhos)

In fact, aryl tosylates and aryl mesylates which are relatively inert than aryl halides

can also be used as effective electrophile partners (Scheme 8 and 9).[23,24]



(Scheme 8: Palladium-catalyzed Suzuki coupling of aryl mesylates using CMphos)



(Scheme 9: Palladium-catalyzed Suzuki coupling of aryl tosylates using CMphos)

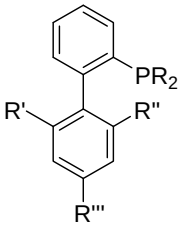
Different electrophilic partners for Suzuki coupling is continuously explored since the Suzuki coupling is considered as one of the most effective methods for the construction of C (sp^2)-C(sp^2) linkages. It is noteworthy for chemists to have further exploration of Palladium-catalyzed Suzuki-Miyaura coupling.

1.3 Phosphine ligands for Suzuki coupling

The development of phosphine ligands plays an important role of transition-metal-catalyzed reactions. The steric and electronic properties of phosphines could have a lot of variation and modification. This allows the fine-tuning of the coordinated species and the enhancement of desired properties of the complex at different steps of catalytic cycle.[25] Phosphine ligands can stabilize and improve the reactivity of catalyst.[26]

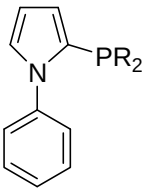
1.3.1. Examples of reported phosphine ligands for Suzuki coupling

Many research groups reported ligands which associated with palladium to perform the Suzuki coupling in low catalytic loading and at high product yield. For example, Buchwald and co-workers had reported a series of biarylmonophosphine which are highly effective for the coupling of a wide range of aryl halides.[27] (Figure 2) Beller's group had reported the use of pyrrole as the scaffold.[28] (Figure 2). Hartwig's group used the ferrocenyl-based dialkylphosphines for cross-coupling.[29] (Figure 2)



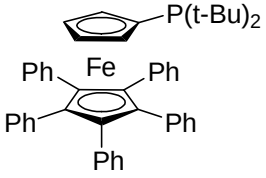
Buchwald group

R = Cy, R', R'', R''' = i-Pr (XPhos)
R = Cy, R', R'' = MeO, R''' = H (S-Phos)
R = t-Bu, R', R'', R''' = H (JohnPhos)
R =Cy, R', R'', R''' = H (CyJohnPhos)



Beller group

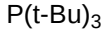
R = Cy, t-Bu



Hartwig group

(Figure 2: Recent development of phosphine ligands having aryl groups)

Besides, some ligands had simpler design on their structure. For example, the Fu and Koie group had reported a tri-tert-butylphosphine ligand.[30]



Fu and Koie group

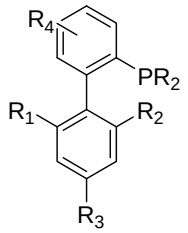
(Figure 3: Recent development of phosphine ligands having alkyl substituents)

The reported ligands for Suzuki coupling share the same feature that most of them consist of a phosphorus atom which binds to the metal atom during catalysis.[31] Those phosphine ligands can be further classified into two categories according to their

structural characteristics. For ligands in figure 1, phosphines having aryl groups at an appropriate position are fixed by their spacers.[32] The other category of phosphine ligands bear three alkyl substituents.(Figure 3) Recently, the dialkylphosphine ligands dominate because of their bulkiness and electron-richness.

1.3.2. Rationale of dialkylphosphine-ligand design

In order to understand the ligand design, the general structure of Buchwald group's ligand was demonstrated:



Buchwald group

(Figure 4: Using Buchwald group as an example of ligand's design)

The alkyl group attached to phosphorus atom plays an important role of determining the electron density on phosphine.[33] The electron density on phosphine is critical for catalysis since the phoshphine binded to the metal center donates the electron to the σ^* orbital of C-X bond to undergo the oxidative addition. In addition, the size of alkyl groups can facilitate the reductive elimination. Most of the reported ligands consisted of dicyclohexylphosphine or ditert-butylphosphine, since they are relatively bulky and electron rich.[34]

The upper aryl ring increases the size of ligand that can stabilize the ligand during catalysis and facilitate the reduction elimination.[35] Substituted groups, R_4, can be

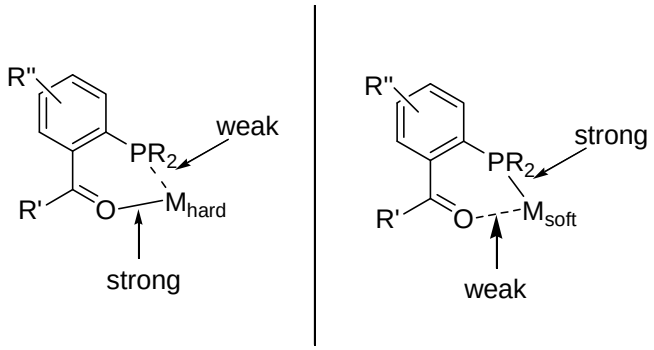
added to fine-tune the electronic density on phosphorus atom or further increase the size of ligand.[36]

The lower aryl ring is used to allow the stabilization of Pd-arene interaction[37] and increase the size of ligand, resulting in faster reductive elimination.

The basic rationale of designing a ligand is the same, however, we are able to generate different type of ligands with a lot of variations, such as changing the scaffold, dialkylphosphine or substituted groups on the ligands.

1.4 Examples of P,O-typed phosphine ligands

P,O-type ligands are a kind of mixed-donor ligands consisting hard and soft donor atoms. They are a class of hemilabile ligands in which a hard (O) and soft (P) atoms bind to the metal in opposite manner.[38] The hard atom, O, binds to hard metal with strong coordination while the interaction between the hard metal and soft donor atom, P, is relatively weak (Figure 5).



(Figure 5: Comparison of binding mode towards hard and soft metal)

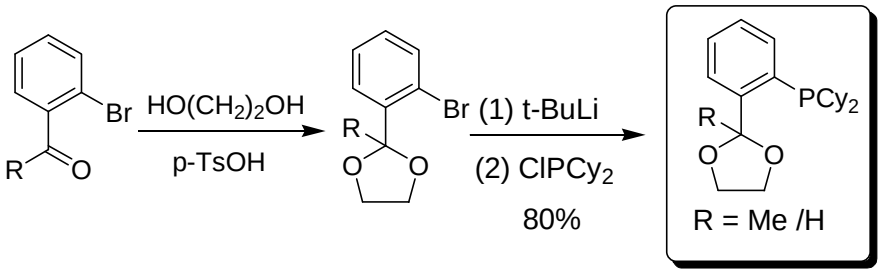
The situation is vice versa for soft metal. The weakly coordinated atom can be easily

dissociated whenever demanded and could exert a dynamic "on and off" mechanism.[39] This property is highly tunable and contributes to generate vacant site for the coordination of substrate and the donor atoms can provide unique reactivity to the metal complexes.[40]

The diversities of the P,O-type ligands are wide that the ligands can couple with different group, such as acetyl group, sulfonyl group and amido group. And its electronic properties and steric properties can be fine-tuned by changing the substituted group on the aryl ring and the bottom group.

1.4.1. P,O-type ligands with acetyl group

In 1999, Guram/Bei et al. from Symyx Technologies reported a P,O-type ligands with acetyl group for Suzuki-Miyaura cross-coupling reactions of aryl chlorides.[41] The ligand was prepared from 2'-bromoacetophenone and 2'-bromobenzaldehyde which are commercially available (Scheme 10).

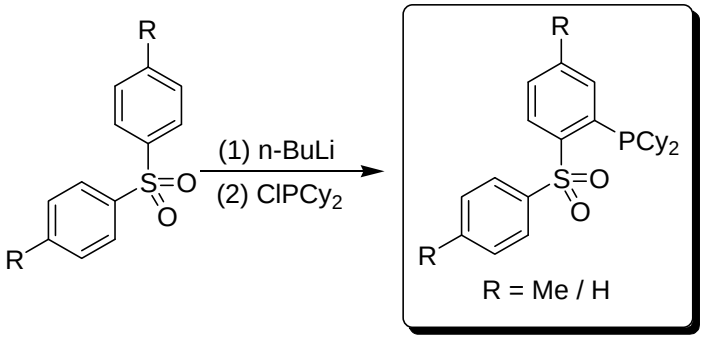


(Scheme 10: Synthesis of hemilabile ligand with acetyl group)

When the R group is methyl, the ligand is effective to the construction of the C-N bond coupling reactions through the amination of aryl chloride.[42]

1.4.2. P,O-type ligands with sulfonyl group

In 2004, Singer/Tom et al. from Pfizer reported a new sulfone type ligand which contained a hemilabile sulfonyl oxygen and a dialkylphosphino group.[43]

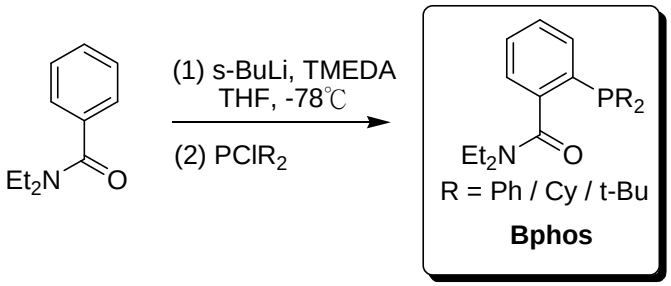


(Scheme 11: Synthesis of P,O-type ligand with sulfonyl group)

The mono-phosphine ligands were prepared by one step through ortho-metallation in which commercially available phenylsulfone or substituted diarylsulfones react with *n*-BuLi and followed by the addition of the chlorodialkylphosphines (Scheme 11). The ligand is effective to the amination of aryl bromide.

1.4.3. P,O-type ligands with amido group

In 2004, Kwong reported P,O-type ligands with amido group which are highly effective for Suzuki-Miyaura coupling of aryl chloride and amination of unactivated aryl chloride.[44] Those ligands are directly synthesized from commercially available *N*,*N*-diethylbenzamide (Scheme 12) through ortho-lithiation protocol which was explored by Beak and Snieckus.[45]

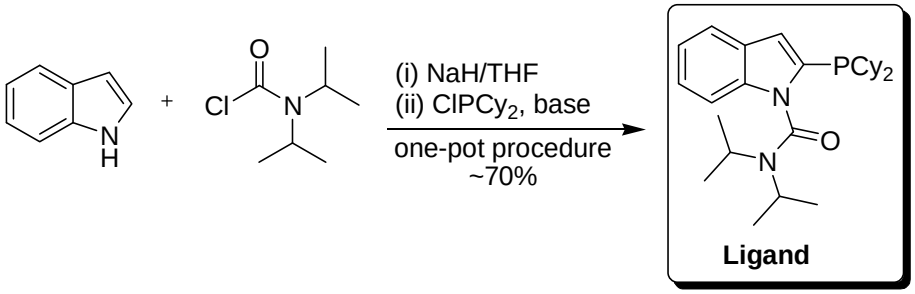


(Scheme 12: Synthesis of P,O-type ligand with amido group)

When the R groups are Cy or t-Bu, the biaryl product formed in excellent yield with low catalyst loading at 60℃.

1.4.4. Indolyl phosphine ligands

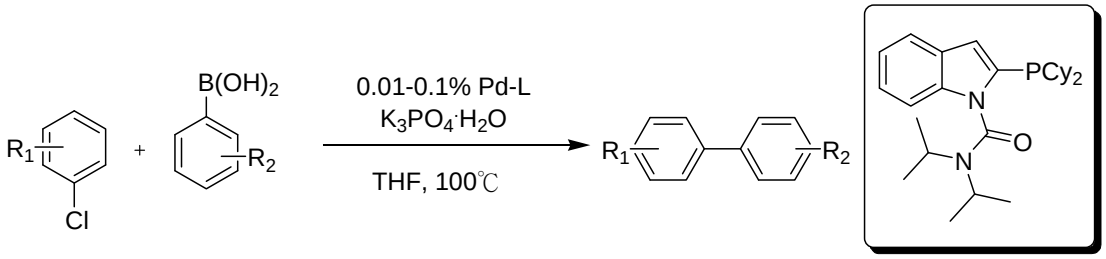
In 2008, Kwong's research group reported a new family of highly tunable indolyl phosphine ligands.[46]

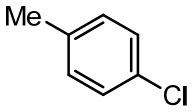
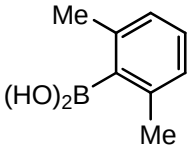
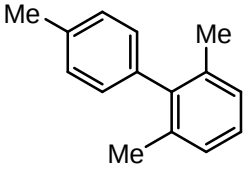
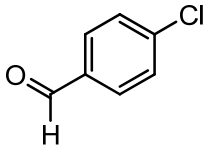
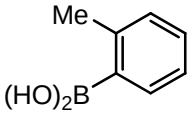
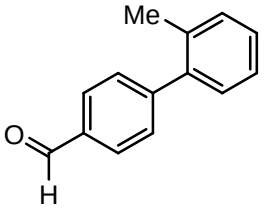
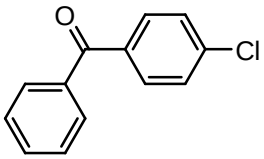
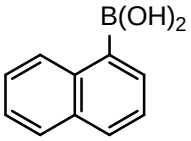
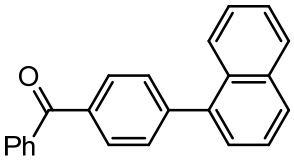
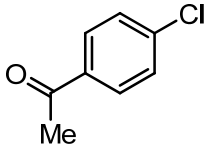
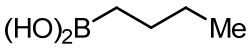
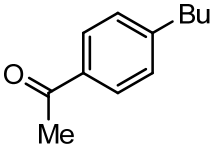


(Scheme 13: Synthesis of indolyl phsophine ligand)

The ligand was highly effective in Suzuki-Miyaura cross-coupling of both aryl and heteroaryl chlorides with aryl boronic acid and the Pd-catalyst loading can be down to 0.01%. The coupling of deactivated chlorides with aryl boronic acid provided good yield with moderate catalyst loading.

TABLE 1: Palladium-Catalyzed Suzuki-Miyaura Coupling of ArCl[a]



entry	ArCl	Ar'B(OH)$_2$	Product	mol% Pd	%yield[b]
1				0.067	81
2				0.01	90
3				0.025	93
4[c]				0.05	87

[a] Reaction conditions: ArCl (1.0 mmol), Ar′B(OH)$_2$ (1.5 mmol), $K_3PO_4 \bullet H_2O$ (3.0 mmol), $Pd(OAc)_2$/L = 1:3, and THF (3.0 mL) were stirred for 24 h at 100 °C under nitrogen. [b] Isolated yields. [c] Reaction conditions: ArCl (1.0 mmol), *n*-BuB(OH)$_2$ (2.0 mmol), $K_3PO_4 \bullet H_2O$ (3.0 mmol), $Pd(OAc)_2$/L = 1:3, and toluene (3.0 mL) were stirred for 24 h at 100 °C under nitrogen.

1.5 Summary

Suzuki coupling is applicable in many fields, such as pharmaceutical industries and polymer, and it is one of the most effective methods of constructing carbon-carbon bond. It is noteworthy that chemists research on the improvement and expansion of the scope of Suzuki coupling. There are countless journals reported the palladium-catalyzed Suzuki coupling. Apart from the metal, ligands play an important role in the cross-coupling. Recently, the reported ligands for Suzuki coupling are mainly bulky and electron-rich dialkylphosphine ligands. These ligands are highly effective since they can facilitate both oxidative addition through electron-richness and reductive elimination through bulkiness of ligands.

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Chapter 2

The study of electronic effects towards the reactivity of indolyl phosphine ligands

2.1. Introduction

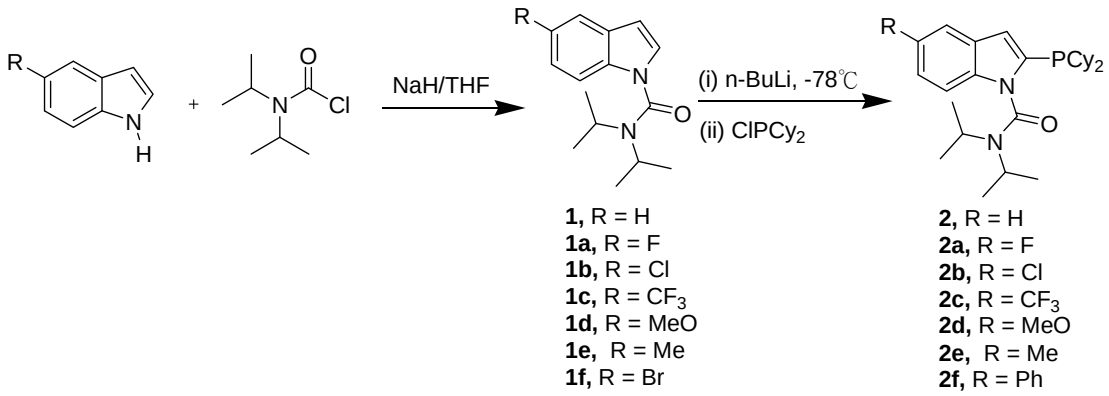
In 2008, our research group published a journal about an indolyl phosphine ligand which is highly effective for the Suzuki coupling of aryl chlorides with arylboronic acid.[1] As an extension of our continuous interest in the ligand, we have been interested in studying the electronic effects towards the reactivity of the ligands. For designing a phosphine ligand, the presence of electron-rich phosphine enhances the rate of oxidative addition while the bulkiness of ligand size increases the rate of reductive elimination.[2] In theory, the reactivity of a ligand is directly proportional to electron density at phosphorus atom.[3]

A series of 5-substituted indolyl phosphine ligands were prepared for the comparison of the electronic effect towards the reactivity of ligand. The purpose of this research is to contribute to the future development and modification of phosphine ligands and to demonstrate the importance of altering the electron density on phosphorus atom by the addition of either electron-donating or electron-withdrawing groups towards the overall reactivity of phosphine ligands.

2.2 Results and discussion

2.2.1. Synthesis of a series of 5-substituted indolyl phosphine ligands

Based on our previous success of developing indolyl phosphine ligand, ligand **2**, which is highly effective for the Suzuki-Miyaura Coupling of aryl chlorides, we synthesized a series of 5-substituted indolyl phosphine ligands in order to test the effect of the electronic effect towards the reactivity of the P,O-type ligand.[4]



(Scheme 1: Synthesis of a series of 5-substituted indolyl phosphine ligands)

By altering the substituted groups on the 5' position on the indole ring, the electron density on phosphorus atom could be changed.[5] All the 5-substituted indoles are commercially available and inexpensive, except the 5-phenyl indole.[6]

For precursor **1f**, it could not be effectively abstracted by directed ortho- metalation (DoM) using *n*-BuLi,[7] since the C-Br will be cleaved before the deprotonation of the 2'position of indole ring, resulting in the addition of PCy_2 into the 5'position of indole ring.

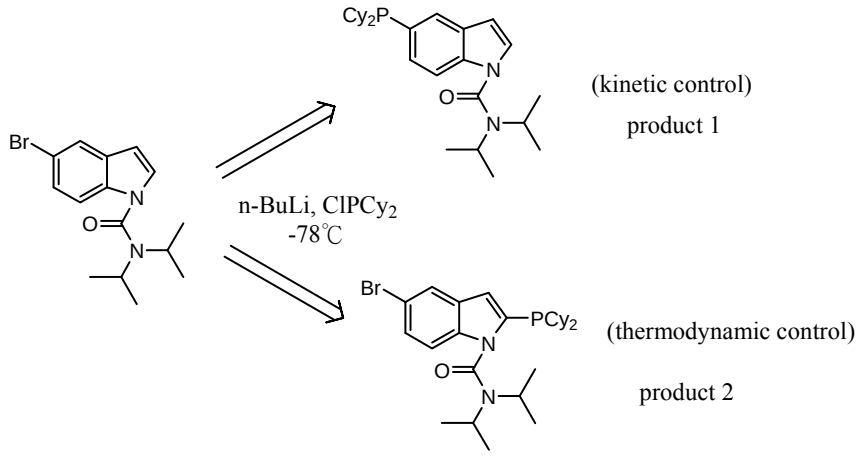
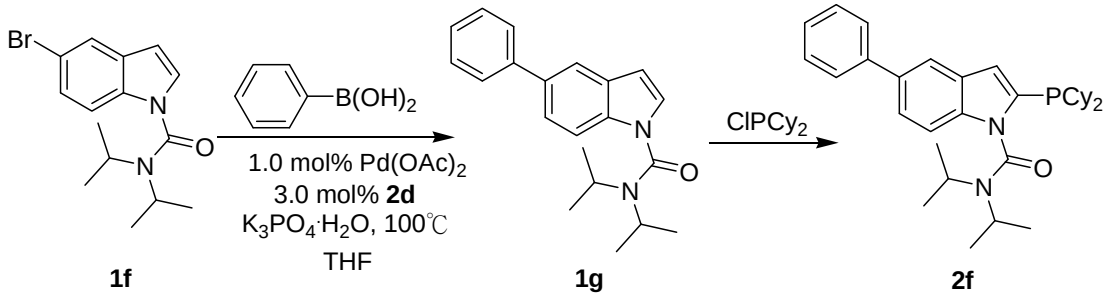


Figure 1. Reaction pathway for precursor **1f**

Since lithiation proceeded under -78℃,[8] kinetic control pathway will dominate and product 1 will be the major product. Therefore, the precursor **1f** was used for the synthesis of 5-phenyl precursor via the coupling of precursor **1f** with phenyl boronic acid.[9] (Scheme 2)



(Scheme 2: Synthesis of 5-phenyl indolyl phosphine ligand)

Table 1: Ligands' yield and their corresponding ^{31}P NMR

Ligand	R	Precursor (% yield)	Ligand (% yield)	^{31}P NMR
2	H	--	--	-22.132
2a	F	52	56	-21.563
2b	Cl	70	79	-21.635
2c	CF_3	85	50	-21.786
2d	MeO	88	69	-21.835
2e	CH_3	69	67	-25.199
2f	Ph	82	64	-21.904

Theoretically, the more electron donating substitute group leads to a more negative ^{31}P NMR chemical shift indicating the higher electron density on the phosphine atom. The electron donating effect should be expected as follow:

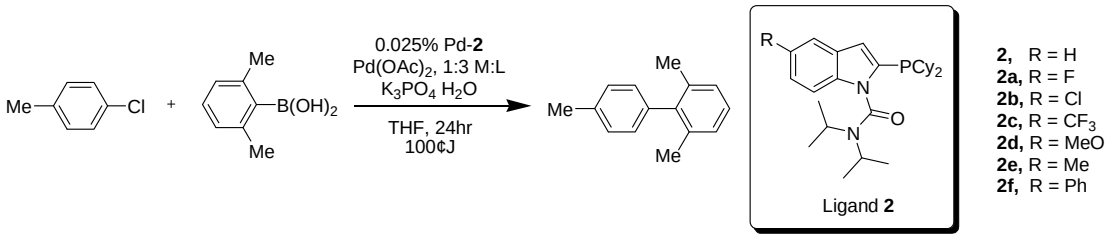
$$MeO > CH_3 > H > Cl > F > Phenyl > CF_3$$

However, the experimental results fail to show the expected trend of ^{31}P NMR. The possible reason is that the distance between the substituted group on 5' position of indole ring and the phosphorus atom is too far. Therefore, the electronic effect is not significant.

2.2.2. Ligand screening

To compare the reactivity of a series of 5-substituted indolyl phosphine ligands, the coupling between the sterically hindered 2,6-dimethyl boronic acid and 4-chlorotoluene was used as the benchmark reaction. From our journal published in 2008, it showed that ligand **2** was able to perform the same reaction with 0.067% mol of $Pd(OAc)_2$ to give 92% of desired product. To demonstrate the difference in reactivity between the 5-substituted phosphine ligands, the catalyst loading of the reaction was set to 0.025% mol of $Pd(OAc)_2$, so as to prevent the complete conversion of the starting material into product.

Table 2: The reactivity of a series of 5-substituted indolyl phosphine ligands



entry	Ligand	R	Conversion %[a]	% yield of product[a]
1	**2**	H	77	76
2	**2a**	F	61	54
3	**2b**	Cl	49	43
4	**2c**	CF_3	42	36
5	**2d**	MeO	82	82
6	**2e**	Me	80	80
7	**2f**	Ph	78	55

[a] GC yield were repeated, average of two trials and using dodecane as internal standard.

The result showed that 5-MeO indolyl phosphine ligand has the highest reactivity among the other 5-substituted ligands. It is reasonable that the phosphine atom of 5-MeO ligand is the most electron-rich and the ligand can effectively donate electron to σ^* orbital of C-Cl, resulting in faster oxidative addition.[10] However, the difference in the reactivity is not obvious for the substituted ligands containing electron-donating groups at the 5' position of the indole ring. The reactivity for ligand **2**, **2d** and **2e** are 76%, 82% and 80% respectively. It is probably because the ligand **2** without substituted group is already electron-rich enough to cleave the C-Cl bond. Further enhancing the electron density on the phosphine atom has slight improvement on the reactivity of the indolyl phosphine ligand.

However, the addition of the electron-withdrawing group on the indole ring has

significant inhibition on the reactivity of the indolyl phosphine ligands. From the table, the reactivity for ligand **2c** is only 36% which is less than the half of ligand **2** containing no substitution on the indole ring. The reactivity for other substituted ligands containing electron-withdrawing group ranged between 43% and 55%. Our finding showed the importance of the electron density on the phosphorus atom towards the reactivity of a ligand. For many cross coupling, such as amination,[11] Heck reaction,[12] oxidative addition is one of the rate-determining step[13] and it depends on the amount of the electron available for donation to anti-bonding orbital of electrophile.

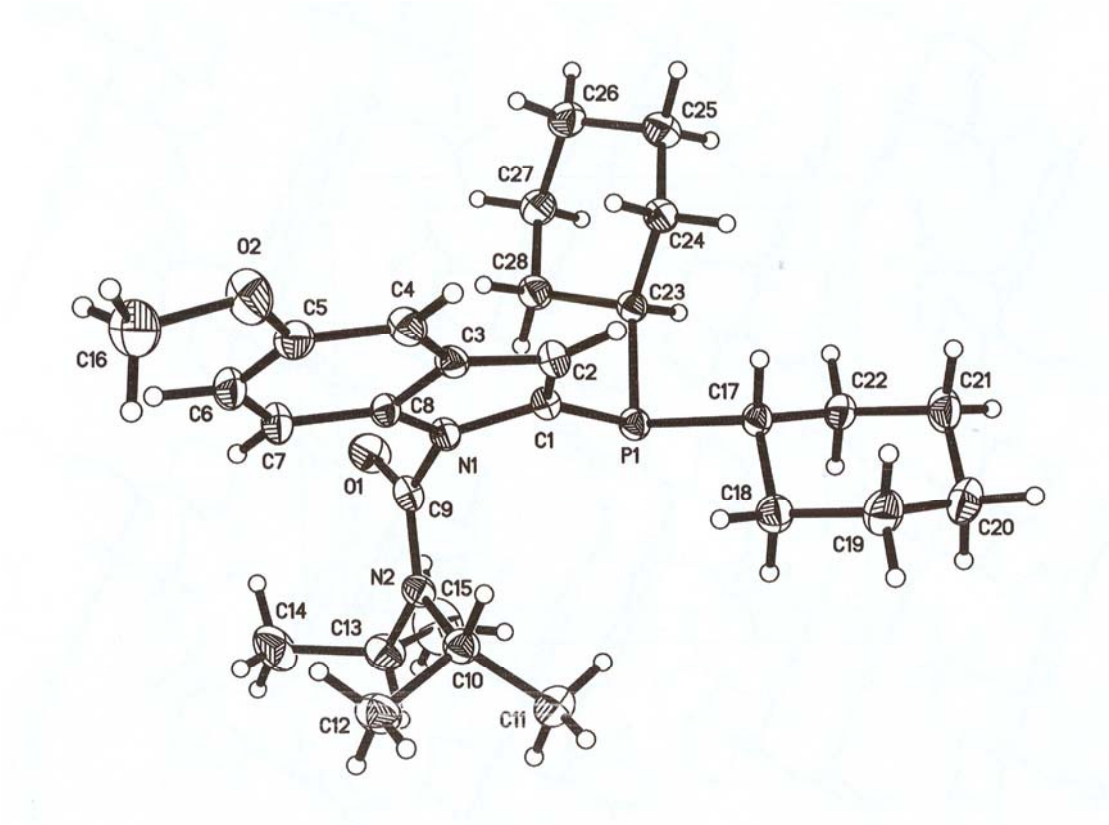
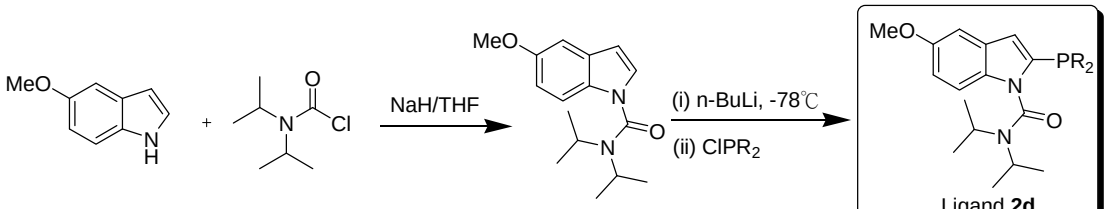


Figure 2. X-Ray structure of ligand **2d**, 5-MeO indolyl phosphine ligand

2.2.3. Synthesis of a family of 5-MeO indolyl dialkylphosphine ligands

After the discovery of the 5-MeO indole as a better scaffold, we synthesize a family of 5-MeO indolyl phosphine ligands to find out the best dialkylphosphine for that scaffold.

Table 3: The percentage yield of a series of 5-MeO indolyl dialkylphosphine ligands



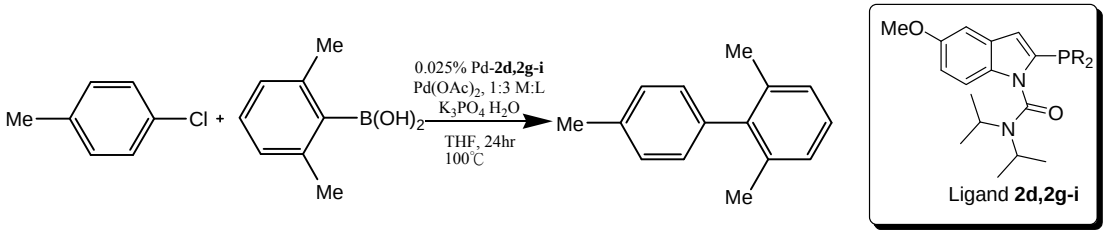
2d, R = Cy
2g, R = t-Bu
2h, R = i-Pr
2i, R = Ph

entry	Ligand	R	Ligand (% yield)
1	**2d**	Cy	69
2	**2g**	t-Bu	71
3	**2h**	i-Pr	75
4	**2i**	Ph	65

2.2.4. Phosphino moiety screening

To test the effectiveness of the 5-MeO ligands, the previous benchmark reaction was used to compare their reactivity.

Table 4: The reactivity of a series of 5-MeO indolyl dialkylphosphine ligands



2d, R = Cy
2g, R = t-Bu
2h, R = i-Pr
2i, R = Ph

entry	Ligand	R	Conversion%[a]	% yield of product[a]
1	**2d**	Cy	82	82
2	**2g**	t-Bu	37	32
3	**2h**	i-Pr	54	48
4	**2i**	Ph	trace	trace

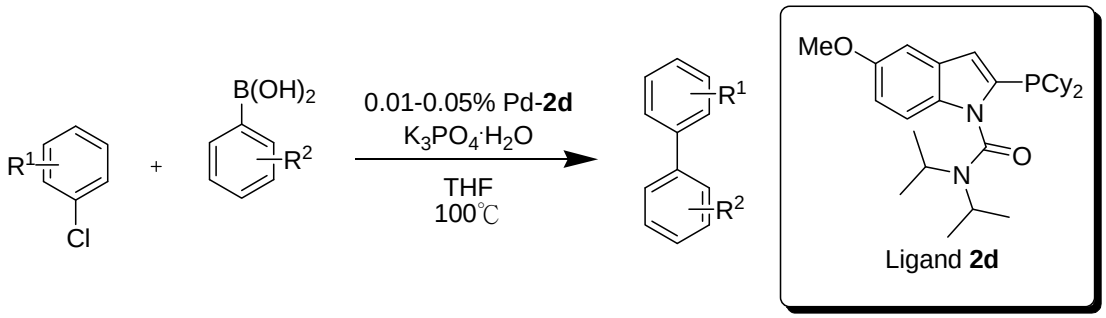
[a] GC yield were repeated, average of two trials and using dodecane as internal standard.

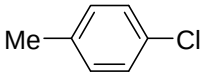
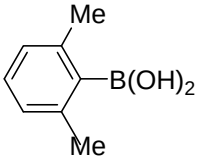
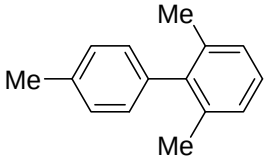
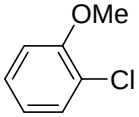
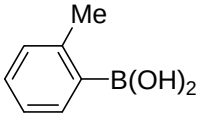
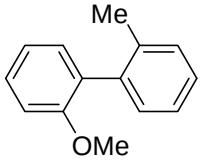
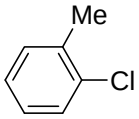
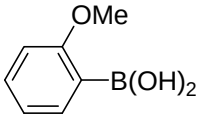
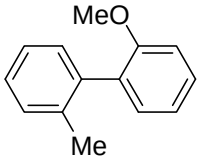
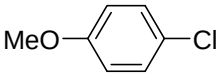
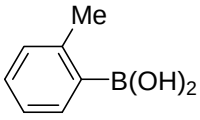
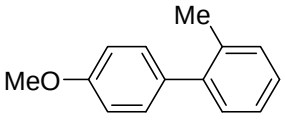
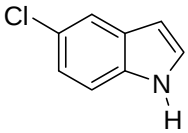
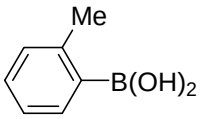
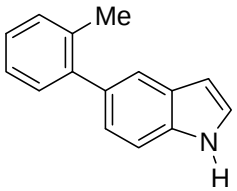
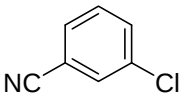
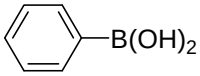
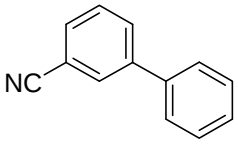
The table showed that the dicyclohexylphosphino analogue was the best partner for the 5-MeO scaffold. The highest catalytic activity for ligand **2d** may be explained by the electron richness of the cyclohexylphosphine.[14] Ligand **2i** with diphenylphosphino moiety had almost no reactivity while ligand **2g** bearing a sterically congested and electron-donating di-*tert*-butylphosphino has lower reactivity than the half of ligand **2d**.[15] Ligand **2h** having di-isopropyl phosphino showed a better reactivity than ligand **2g**. After finding out the ligand **2d** as the best ligand among the others, a wide range of activated and deactivated aryl chlorides were coupled with arylboronic acid in order to show the substrate scopes and demonstrate the reactivity towards various substrates combination, using the same optimized reaction conditions.

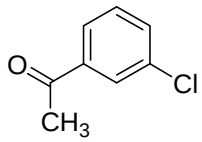
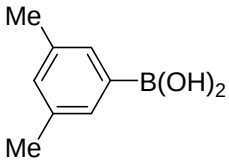
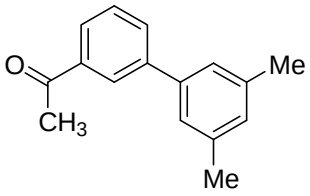
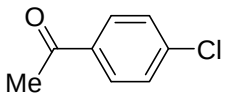
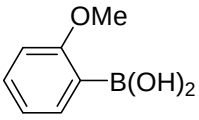
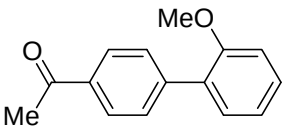
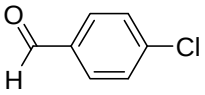
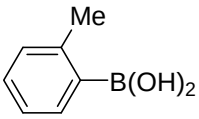
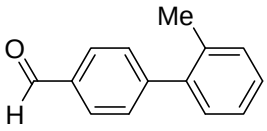
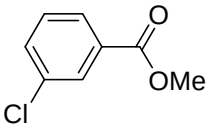
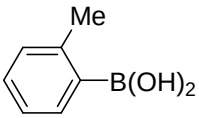
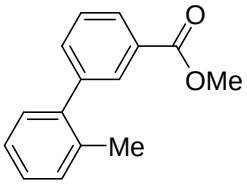
2.2.5. Palladium-Catalyzed Suzuki-Miyaura Coupling of both activated and deactivated aryl chlorides

Compared to ligand **2** having no substituted group on the ring, ligand **2d** has slight improvement in using lower catalytic loading to perform the coupling of same substrates (Table 5).

Table 5: Palladium-Catalyzed Suzuki-Miyaura Coupling of ArCl[a]



Entry	ArCl	Ar'B(OH)$_2$	Product	Mol% Pd	%yield[b]
1				0.033	85
2				0.05	93
3				0.05	83
4				0.05	87
5				0.05	91
6				0.02	90

7				0.02	93
8				0.01	87
9				0.01	94
10				0.01	83

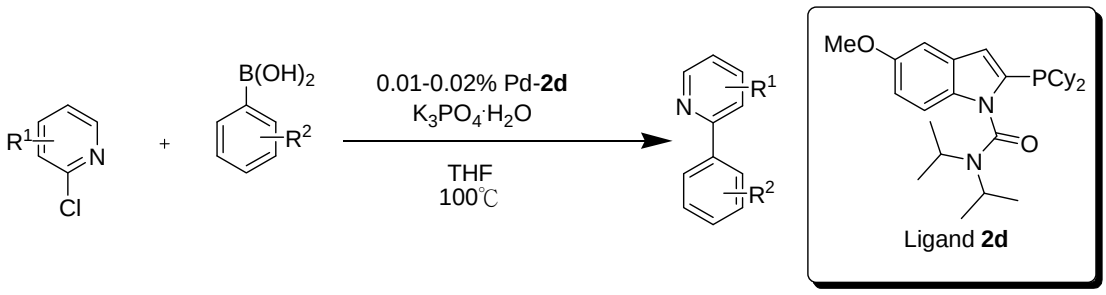
[a] Reaction conditions: ArCl (1.0 mmol), Ar'$B(OH)_2$ (1.5 mmol), $K_3PO_4 \bullet H_2O$ (3.0 mmol), $Pd(OAc)_2$/L = 1:3, and THF (3.0mL) were stirred for 24 h at 100℃ under nitrogen. [b] Isolated yields.

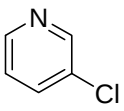
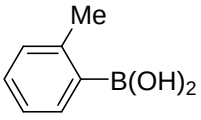
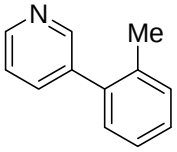
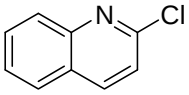
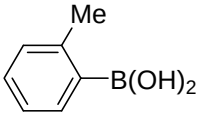
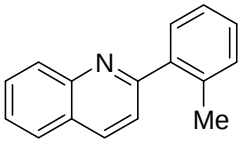
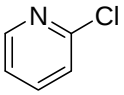
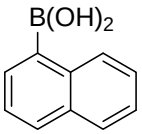
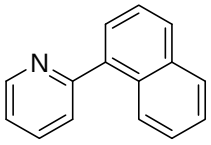
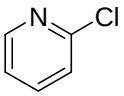
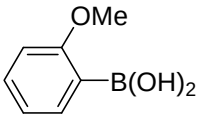
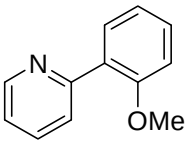
For the coupling of deactivated aryl chlorides, entry 1-4, the catalyst loading ranged from 0.033%-0.05% mol of Pd. Apart from the deactivated aryl chlorides, the ligand **2d** was able to catalyze the coupling of activated aryl chlorides bearing function groups, such as keto, aldehyde, ester and nitriles, with extremely low catalyst loading ranging from 0.01% to 0.05%. Most of the coupling reactions could be generally performed with 0.01% catalyst loading. The presence of functional groups weakened the strength of C-Cl bond, resulting in the requirement of extremely low catalyst loading. For entry 5, the proton on the 1' position of indole ring could be tolerated during the catalysis and the catalyst loading and product yield were satisfactory.

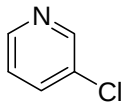
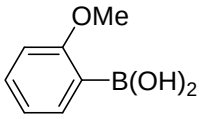
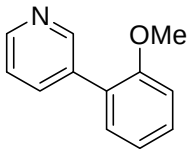
2.2.6. Palladium-Catalyzed Suzuki-Miyaura Coupling of heteroaryl chlorides

In addition, ligand **2d** was highly effective for coupling of heteroaryl chlorides with arylboronic acid and the catalyst loading could be generally down to 0.01% mol Pd. (Table 6)

Table 6: Palladium-Catalyzed Suzuki-Miyaura Coupling of Heteroaryl Chlorides[a]



Entry	ArCl	Ar'B(OH)$_2$	Product	Mol% Pd	%yield[b]
11				0.02	93
12				0.01	97
13				0.01	94
14				0.01	95

15				0.01	85

[a] Reaction conditions: ArCl (1.0 mmol), Ar'$B(OH)_2$ (1.5 mmol), $K_3PO_4 \bullet H_2O$ (3.0 mmol), $Pd(OAc)_2$/L = 1:4, and THF (3.0mL) were stirred for 24 h at 100℃ under nitrogen. [b] Isolated yields.

The optimal reaction conditions for the coupling of heteroaryl chlorides were the same, except the ratio of metal to ligand. The ratio was set at 1 to 4 and more ligand was required to compete the vacant sites of Palladium metal with substrates. The lone pair electron of nitrogen atom in heteroaryl chlorides was able to bind with the metal. Therefore, more ligands were required to force the substrate out from the metal and occupy the vacant sites on metal.

2.3 Conclusion

In summary, we have synthesized a series of 5-substituted indolyl phosphine ligands to study the electronic effect towards the reactivity of P,O-type ligand. From our research, it revealed that the addition of electron-donating group on the 5'position on indole ring could enhance the electron density on phosphorus atom and resulted in the slight improvement of the reactivity of ligand. However, the introduction of electron-withdrawing group would greatly inhibit the reactivity of ligand. The research finding will be an important reference for the future development of phosphine ligands and it showed the importance of the electron density on phosphorus atom which plays an important role of the oxidative addition during the catalysis. We anticipate that we can apply the principle into our future ligands' design and modification.

2.4 Experimental section

General Procedure for Suzuki-Miyaura Coupling of aryl chlorides: $Pd(OAc)_2$ (2.3 mg, 0.010 mmol) and ligand (0.030 mmol) were loaded into an oven-dried Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three times. Precomplexation was applied by adding freshly distilled THF into the tube. The solution was stirred for about 1 to 2 minutes until all the metal and ligand were dissolved in the solvent. Aryl chlorides (1.0 mmol), arylboronic acid (1.5 mmol), and $K_3PO_4 \bullet H_2O$ (3.0 mmol) were loaded into another Schlenk tube, and the system was further evacuated and flushed with nitrogen three times. The solvent THF (2.0 ml) was added, following the addition of catalyst dissolved in THF. The total volume of THF in the catalytic system is 3ml. The tube was stirred at room temperature for several minutes and then placed into a preheated oil bath (100 °C) for the time period as indicated in the tables. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and quenched with water and diluted with Ether. The organic layer was separated and the aqueous layer was washed with Ether twice. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

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Chapter 3

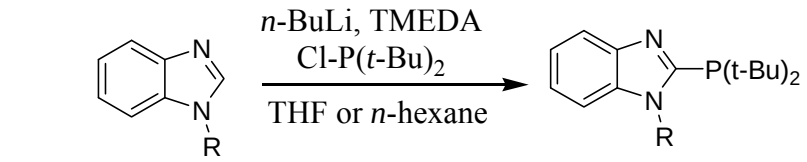
Newly Developed Benzimidazole-Based Phosphine Ligands for Palladium-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides

3.1. Introduction

Continuing with the previous research of the synthesis of the indolyl phosphine ligands in 2008,[1] we further explore the use of benzimidazole as the scaffold of ligands. Benzimidazole is chosen since it is commercially available and reasonable priced. In addition, the precursors of ligands are easily deprotonated since there is only one proton at the 2' position of benzimidazole. During the synthesis of ligands, less side products will be formed, resulting in atom economy.[2] For modification, the reactivity of ligands can be modified by the addition of substituted groups into the benzimidazole ring.[3]

The research idea of using benzimidazole came from Matthias Bella, in 2004, who published the use of dialkylphosphinoimidazoles as new ligands for Suzuki Miyaura coupling of aryl chlorides with general catalyst loading 0.05 mol%Pd[4] and however, the metal to ligand ratio is too high (1:10). *N*-Arylbenzimidazoles were prepared by a copper-catalyzed *N*-arylation of benzimidazole. The obtained *N*-arylated benzimidazoles were then deprotonated by a mixture of *n*-BuLi and TMEDA in

n-hexane or THF (Scheme 1).



R = Ph, Naphthalene

L1: R = Ph, 41%
L2: R = Naphthalene, 33%

(Scheme 1: Synthesis of *N*-aryl-2-(dialkylphosphino)benzimidazoles)

From the idea of Beller, we combine the benzimidazole, hemilabile *N*,*N*-diisopropyl carbamoyl group and dialkylphosphino group together to generate a series of newly developed benzimidazole-based phosphine ligands. The ligands were applied to the Suzuki-Miyaura coupling of aryl chlorides.

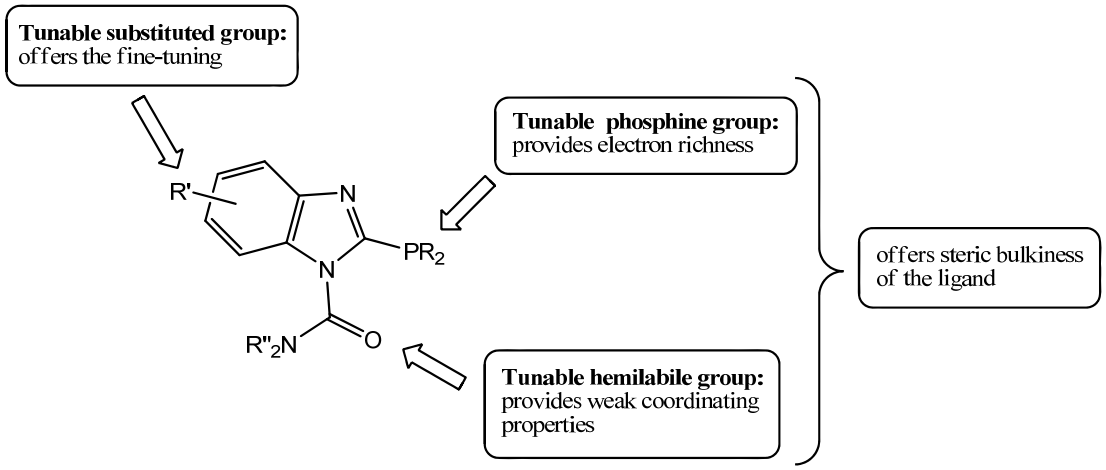
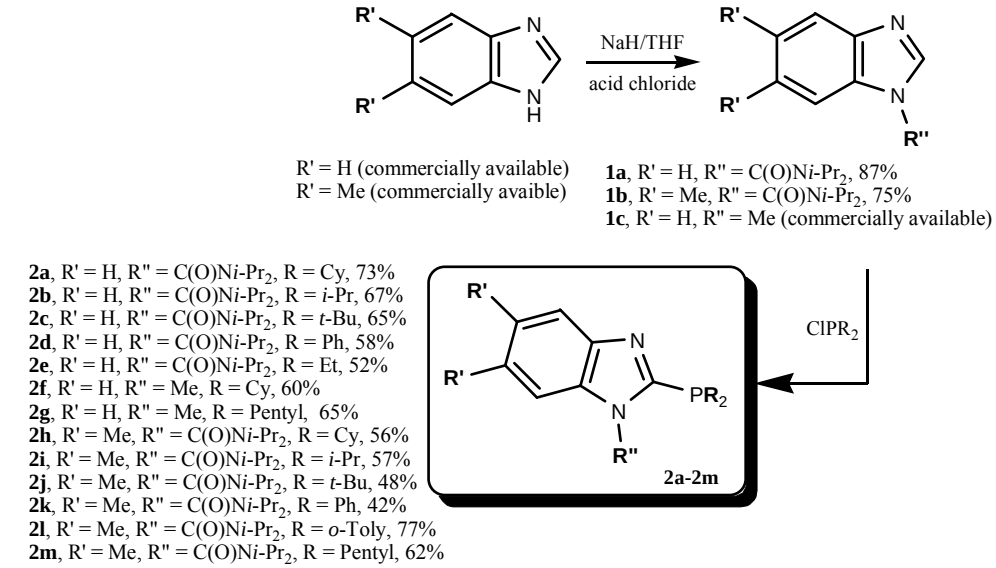


Figure 1. Strategic design of an easily diversified phosphine ligand family

Literature reports concerning the use of benzimidazole as ligands' scaffold are limited.[5] Therefore the use of benzimidazole for the synthesis of ligand will be a new direction and there will be a lot of room to explore.

3.2. Results and Discussion

3.2.1. Preparation of ligands



(Scheme 2: General picture of the synthesis of a family of benzimidazole-based phosphine ligands)

The synthesis of the benzimidazole-based phosphine ligands was a two-step process. The starting materials, benzimidazole or 5,6-dimethyl benzimidazole, were reacted with the *N*,*N*-diisopropylcarbomyl chloride through condensation reaction. Then the purified precursors were lithiated by *n*-BuLi under -78℃,[6] following the trapping of dialkylphosphine to generate various ligands.[7] (Scheme 2) The yields of precursor and ligand were shown as follow:

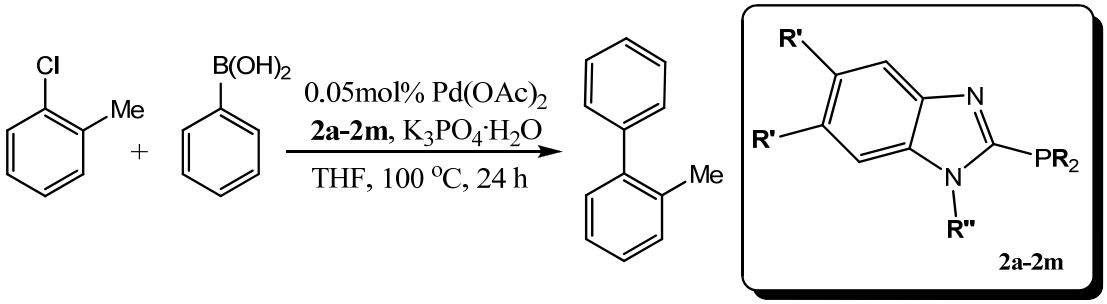
Table 1: Ligands' yield and their corresponding ^{31}P NMR

Entry	Ligand	Precursor % yield	Ligand % yield	Chemical shift of ^{31}P NMR
1	**2a**		73	-15.95
2	**2b**		67	-7.66
3	**2c**	87	65	14.35
4	**2d**		58	-25.44

5	**2e**		52	-28.99
6	**2f**	N/A	60	-22.55
7	**2g**		65	-24.34
8	**2h**		56	-16.35
9	**2i**		57	-8.07
10	**2j**		48	13.95
11	**2k**	75	42	-25.66
12	**2l**		77	-39.43
13	**2m**		62	-19.70

3.2.2. Ligands screening

Table 2: Investigation on the effectiveness of the benzimidazolylphosphine ligands 2 in Suzuki-Miyaura coupling of nonactivated ArCl[a]



entry	ligand	%yield[b]
1	**2a** (R' = H, R" = C(O)N*i*-Pr$_2$, R = Cy)	43
2	**2b** (R' = H, R" = C(O)N*i*-Pr$_2$, R = *i*-Pr)	18
3	**2c** (R' = H, R" = C(O)N*i*-Pr$_2$, R = *t*-Bu)	8
4	**2d** (R' = H, R" = C(O)N*i*-Pr$_2$, R = Ph)	0
5	**2e** (R' = H, R" = C(O)N*i*-Pr$_2$, R = Et)	0
6	**2f** (R' = H, R" = Me, R = Cy)	18
7	**2g** (R' = H, R" = Me, R = Pentyl)	9
8	**2h** (R' = Me, R" = C(O)N*i*-Pr$_2$, R = Cy)	57
9	**2i** (R' = Me, R" = C(O)N*i*-Pr$_2$, R = *i*-Pr)	23
10	**2j** (R' = Me, R" = C(O)N*i*-Pr$_2$, R = *t*-Bu)	13
11	**2k** (R' = Me, R" = C(O)N*i*-Pr$_2$, R = Ph)	0
12	**2l** (R' = Me, R" = C(O)N*i*-Pr$_2$, R = *o*-Toly)	0
13	**2m** (R' = Me, R" = C(O)N*i*-Pr$_2$, R = Pentyl)	38

[a] Reaction conditions: ArCl (1.0 mmole), $PhB(OH)_2$ (1.5 mmole), $K_3PO_4 \bullet H_2O$ (3.0 mmole),

$Pd(OAc)_2$/L = 1:2, and THF (3 mL) were stirred for 24 h at 100°C under nitrogen. [b] Calibrated GC yields were reported using dodecane as the internal standard.

The coupling between 2-chlorotoluene and phenyl boronic acid was applied as benchmark reaction for the comparison of the ligands' reactivity. The reaction conditions were fixed to use 0.05 mol% of $Pd(OAc)_2$ with metal to ligand ratio 1:2, together with $K_3PO_4 \bullet H_2O$ as base and THF as solvent.

From the table 2, ligand **2h** and **2a** showed the greatest and the second greatest reactivity respectively among the other ligands. The possible reasons were that dicyclohexylphosphino moiety was sufficiently electron-rich to facilitate the donation of electron from phosphine atom to the C-Cl bond.[8] In addition, the bulky size of dicyclohexylphosphino moiety enhanced the rate of reductive elimination.[9]

During oxidative addition, the electron was donated to the σ^* orbital of C-Cl bond for cleavage.[10] The more electron density on phosphine atom, the faster should be the rate of oxidative addition.[11] Ligand **2h** having dimethylbenzimidazole as scaffold had further enhancement of the electron density on the phosphine atom, resulting in faster reactivity than ligand **2a**.

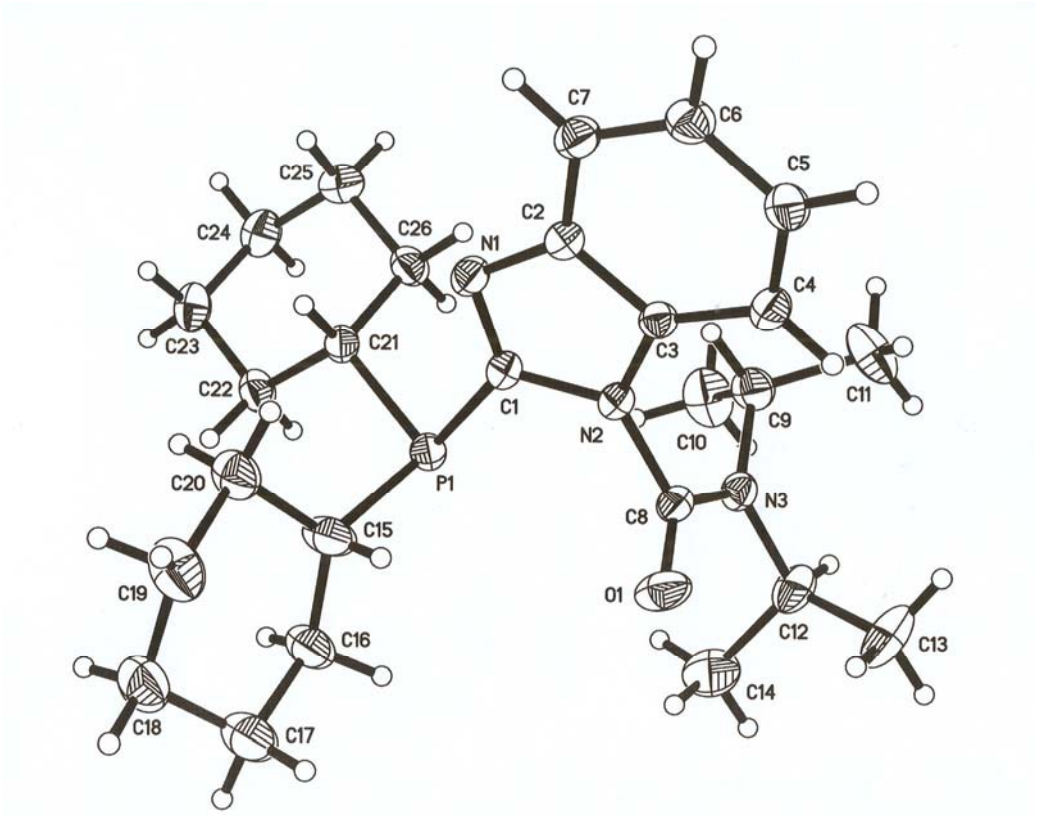


Figure 2. X-Ray structure of ligand **2a**,
Benzimidazole-based dicyclohexylphosphine ligand

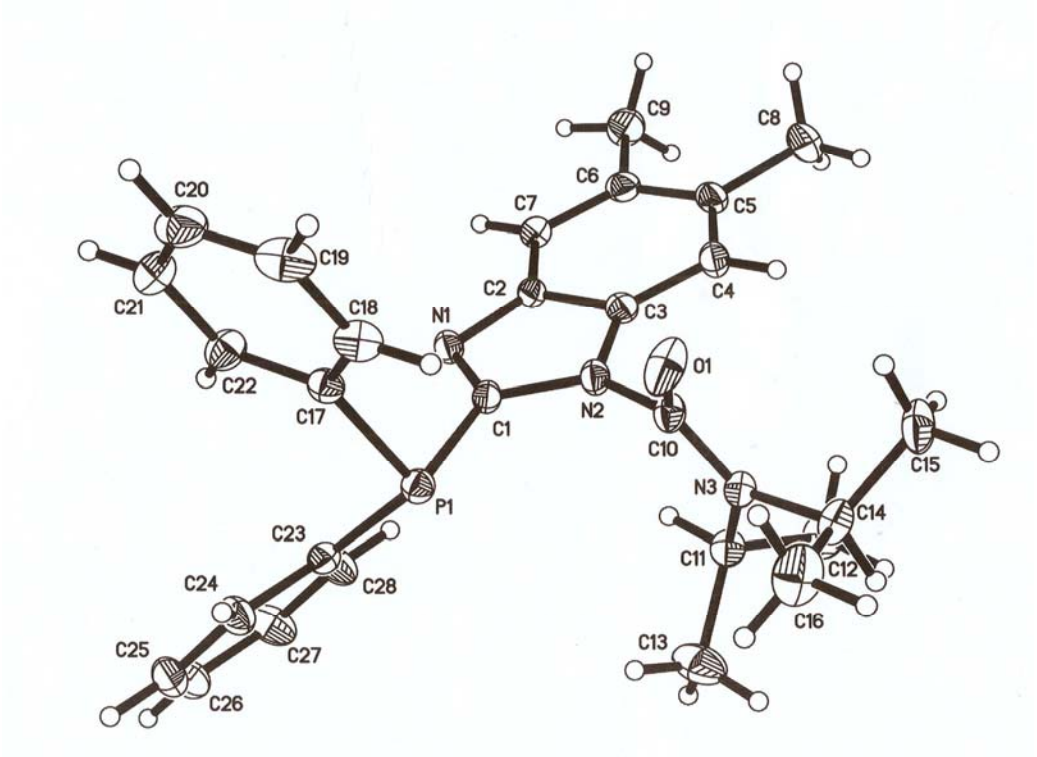


Figure 3. X-Ray structure of ligand **2h**,
Dimethylbenzimidazole-based dicyclohexylphosphine ligand

Ligand **2c** and **2j** both bearing a sterically congested and electron-donating di-*tert*-butylphosphino moiety showed very low product yield towards coupling reaction.[12] Ligand **2b** and **2i** both bearing diisopropylphosphino moiety with similar steric bulkiness as dicyclohexylphosphino moiety afforded lower conversion. Ligand **2d** and **2k** with a diphenylphosphino moiety provided no conversion. It is probably because the π-conjugated system in two phenyl rings decreased the electron richness in coordinated metal center by delocalization. In addition, ligand **2e** bearing a less sterically congested diethylphosphino moiety showed no conversion.

By comparing the ligands **2a** and **2f**, replacing the carbamoyl group by methyl group would greatly inhibit the catalytic activity. This direct comparison demonstrated the importance of the bulky carbamoyl group which acted as a main role of on and off mechanism[13] and probably enhanced the rate of reductive elimination.

3.2.3. The effect of the addition of dimethyl group on scaffold

Table 3: Direct comparison of the effectiveness between ligands 2a-d and 2h-k with various dialkylphosphino moiety

	Ligand (R' = H)	δ of ^{31}P NMR	%yield[a]	Ligand (R' = Me)	δ of ^{31}P NMR	%yield[a]
R = Cy	**2a**	-15.95	43	**2h**	-16.35	57
R = *i*-Pr	**2b**	-7.66	18	**2i**	-8.07	23
R = *t*-Bu	**2c**	14.35	8	**2j**	13.95	13
R = Ph	**2d**	-25.44	0	**2k**	-25.66	0

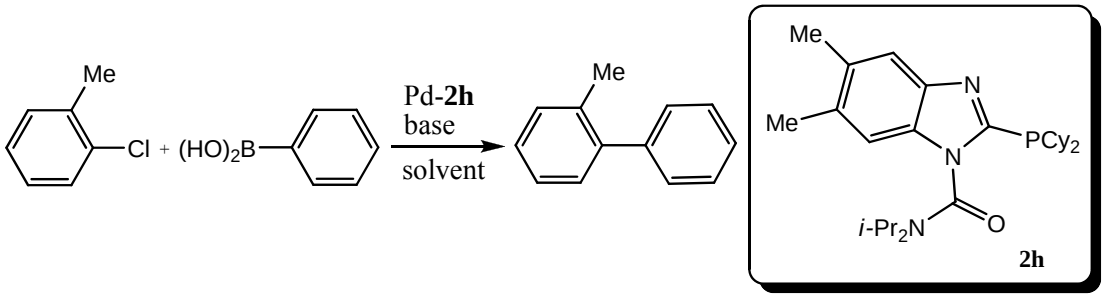
[a] Calibrated GC yields were reported using dodecane as the internal standard.

In order to further enhance the catalytic activity of the newly developed benzimidazole-based phosphine ligands, fine-tuning was made on the scaffold by

incorporating two methyl groups to the 5,6-position of benzimidazole.[14] From table 3, it showed that there was a general enhancement of reactivity among various dialkylphosphino moiety when using 5,6-dimethyl benzimidazole as scaffold. The enhancement of the electron density on phosphine atom was evidenced by the ^{31}P NMR of ligands.[15] The chemical shifts of ^{31}P NMR of ligands **2h-k** were more up-field (value were shifted to negative side) than ligands **2a-d** (Table 2).

3.2.4. Reaction condition screening

Table 4: Optimization of the reaction conditions of ligand **2h**[a]



entry	Pd source	Pd:L	mol% Pd	base	solvent	temp. °C	% yield[b]
1	$Pd_2(dba)_3$	1:2	0.05	$K_3PO_4 \cdot H_2O$	THF	100	44
2	$Pd(OAc)_2$	1:2	0.05	$K_3PO_4 \cdot H_2O$	THF	100	57
3	$Pd(dba)_2$	1:2	0.05	$K_3PO_4 \cdot H_2O$	THF	100	31
4	$PdCl_2$	1:2	0.05	$K_3PO_4 \cdot H_2O$	THF	100	0
5	$Pd(OAc)_2$	1:1	0.05	$K_3PO_4 \cdot H_2O$	THF	100	14
6	$Pd(OAc)_2$	1:2.5	0.05	$K_3PO_4 \cdot H_2O$	THF	100	67
7	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	THF	100	75
8	$Pd(OAc)_2$	1:4	0.05	$K_3PO_4 \cdot H_2O$	THF	100	34
9	$Pd(OAc)_2$	1:5	0.05	$K_3PO_4 \cdot H_2O$	THF	100	32
10	$Pd(OAc)_2$	1:10	0.05	$K_3PO_4 \cdot H_2O$	THF	100	11
11	$Pd(OAc)_2$	1:3	0.05	K_3PO_4	THF	100	55
12	$Pd(OAc)_2$	1:3	0.05	K_2CO_3	THF	100	62
13	$Pd(OAc)_2$	1:3	0.05	Na_2CO_3	THF	100	28
14	$Pd(OAc)_2$	1:3	0.05	Cs_2CO_3	THF	100	4

15	$Pd(OAc)_2$	1:3	0.05	CsF	THF	100	2
16	$Pd(OAc)_2$	1:3	0.05	NaO(t-Bu)	THF	100	0
17	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	Dioxane	100	35
18	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	Toluene	100	17
19	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	t-Butanol	100	13
20	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	THF	r.t.	0
21	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	THF	90	28
22	$Pd(OAc)_2$	1:3	0.05	$K_3PO_4 \cdot H_2O$	THF	110	93
23	$Pd(OAc)_2$	1:3	0.1	$K_3PO_4 \cdot H_2O$	THF	100	91

[a] Reaction conditions: ArCl (1.0 mmole), $PhB(OH)_2$ (1.5 mmole), base (3.0 mmole), and solvent (3 mL) were stirred for 24 h under nitrogen. [b] Calibrated GC yields were reported using dodecane as the internal standard.

In the screening table, several reaction parameters were screened, such as metal source, metal to ligand ratio, base, solvent, temperature and catalyst loading. During the optimization, only one parameter was varied while keeping others constant. The parameter with the highest percentage yield would be chosen for further screening.

Effect of metal source:

$Pd(OAc)_2$ gave the best performance towards coupling reaction (Table 4, entries 1-4) among the other metal sources. $Pd_2(dba)_3$ and $Pd(dba)_2$ are Pd(0) metal sources which require no initial reduction step (entries 1 and 3), but the dissociation of dba is difficult that less vacant site on Pd(0) will be available for ligand binding.[16] Therefore, they are not an effective metal source. Besides, $PdCl_2$ provided no conversion because $PdCl_2$ is insoluble towards the solvent.[17] $Pd(OAc)_2$ was selected as the metal source for further investigations. In addition, $Pd(OAc)_2$ offers a competitive edge that it is relatively air-stable than $Pd_2(dba)_3$ and $Pd(dba)_2$.

Effect of metal to ligand ratio:

From entry 2 and entries 5-10, there was an increasing trend of the product yield when the metal to ligand ratio increased from 1:1 to 1:3. After the optimal ratio, 1:3, the product yield was inversely proportional to the metal to ligand ratio. The product yield was greatly suppressed when the ratio was up to 1:10. The possible reason was that excess amount of ligand might block the coordination of the substrate with the metal during the beginning of metallic cycle, resulting in ineffective catalyst system.[18] The 1:3 ratio was found to be the most suitable metal to ligand ratio for the optimum reactivity of ligand **2h**.

Effect of base:

Seven bases were chosen for comparison and the result revealed that weak bases, such as $K_3PO_4 \bullet H_2O$ (entry 10), K_3PO_4 (entry 11), K_2CO_3 (entry 12), Na_2CO_3, (entry 13), Cs_2CO_3 (entry 14), gave better reactivity than the strong base, CsF (entry 15) and NaO(*t*-Bu) (entry 16). Base plays an important role in transmetallation.[19] Among the weak bases, $K_3PO_4 \bullet H_2O$ showed the best performance.

Effect of solvent:

THF, toluene, dioxane and DMF have different boiling points and solubilities towards the substrates. The unique performance of the solvents is based on the principle of solvent effect.[20] By various solvents surveyed, THF was found to be the most

effective solvent for ligand 2**h** to coupling aryl chlorides with aryl boronic acid.

Effect of temperature:

The reactivity of the ligand increased with the temperature and the reactivity was the highest when the temperature was 110℃ (entry 22). If there is no heat energy applied to the catalysis, the conversion of the coupling reaction was almost zero (entry 20). Heat is an essential factor for coupling reaction to assist the substrate to overcome the activation barrier.

Effect of catalyst loading:

The conversion of the coupling reaction was directly proportional to the amount of the catalyst. However, the catalyst loading should be kept as low as possible while the conversion should be over 90%. The amount of catalyst used reflected the difficulty of coupling of different substrates. In the screening test, 0.05% mol Pd was used to compare the conversion under different reaction conditions. If the catalyst loading was too high or too low, the difference between various reaction conditions was not obvious.

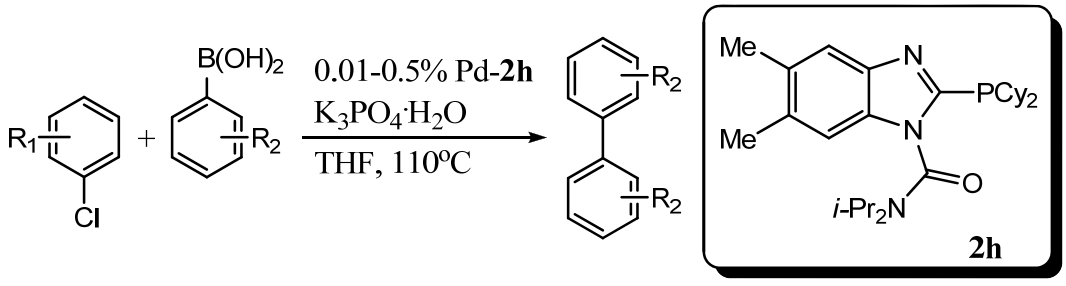
Inter-play between temperature and catalyst loading

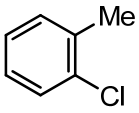
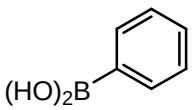
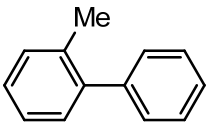
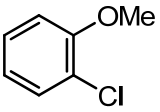
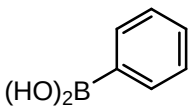
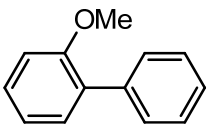
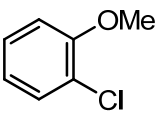
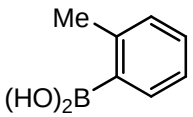
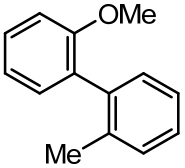
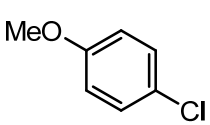
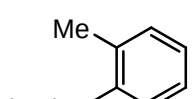
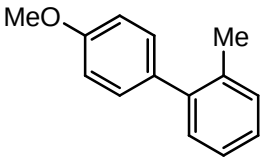
For entry 22 and entry 23, both had above 90% product yield. The differences between two entries were the catalyst loading and the temperature that low catalyst loading with high temperature produced similar performance as high catalyst loading

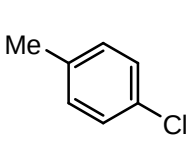
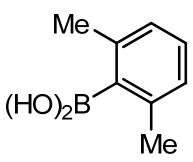
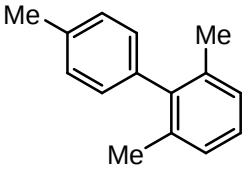
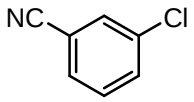
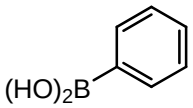
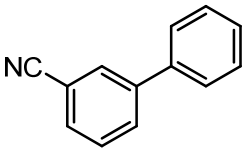
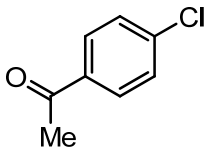
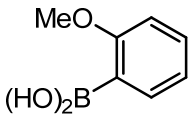
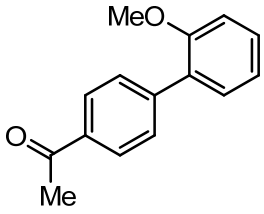
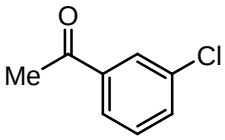
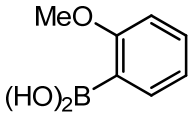
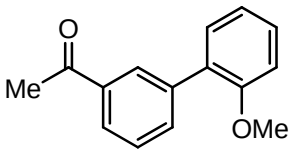
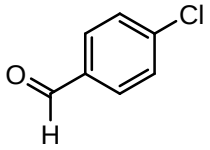
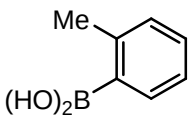
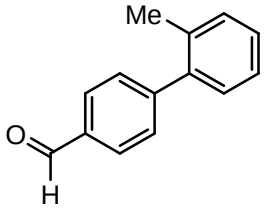
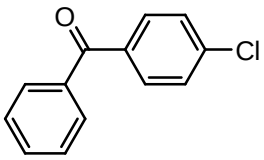
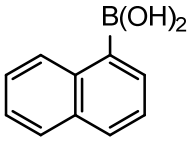
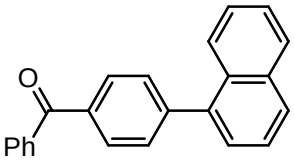
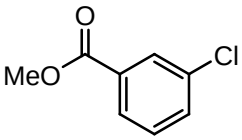
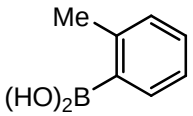
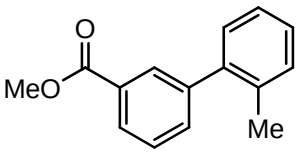
with low temperature. From economic aspect, we had to consider the cost of metal and the cost of temperature. In addition, when we had chosen the use of high temperature, there will be more flexible in adjusting the catalyst loading for other coupling partners. Therefore, 110℃ was selected for our further investigation.

3.2.5. Suzuki-Miyaura coupling of both activated and deactivated ArCl

Table 5: Palladium-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides with Arylboronic Acids[a]



entry	ArCl	Ar'B(OH)$_2$	Product	mol% Pd	%yield[b]
1[c]				0.1%	91
2				0.05%	93
3				0.067	96
4				0.1	86
5				0.1	97

6				0.5	44
7				0.05	>99
8				0.02	81
9				0.05	80
10				0.01	94
11				0.01	81
12				0.025	87

[a] Reaction conditions: ArCl (1.0 mmole), Ar'B(OH)$_2$ (1.5 mmole), $K_3PO_4 \bullet H_2O$ (3.0 mmole), Pd(OAc)$_2$/L = 1:3, and THF (3 ml) were stirred for 24 h at 110°C under nitrogen. [b] Isolated yields. [c] At 100°C

A range of aryl chlorides were examined under the preliminary optimized reaction conditions (Table 5). The deactivated aryl chlorides containing different substituted groups, such as methyl and methoxy group, were coupled with different arylboronic

acids. In the presence of moderate catalyst loading, 0.05-0.1 mol% Pd, sterically hindered aryl chlorides were coupled with arylboronic acids to give excellent product yields (Table 5, entries 2-5). Upon examining the methyl group and methoxy group at the *ortho*-position of the aryl chlorides coupling, a higher catalyst loading was required for 2-chloroanisole substrate (Table 5, entries 2 and 3). Although methoxy group provided less steric hindrance than methyl group, methoxy group provided stronger electronic effect than methyl group to strengthen the C-Cl bond. In this case, the electronic effect became a predominant factor, so higher catalyst loading was required.

On the other hand, when increasing the steric hindrance of arylboronic acids, a higher catalyst loading should be applied to obtain an excellent yield (Table 5, entries 3 and 4). By comparing the effect of different position of methoxy groups, the methoxy group at *para*-position showed higher isolated yield due to less steric hindrance (Table 5, entries 4 and 5). In order to further extend the scope of this new ligand, a highly steric hindered substrate was studied (Table 5, entry 6), however it only had 44% yield at 0.5 mol% catalyst loading.

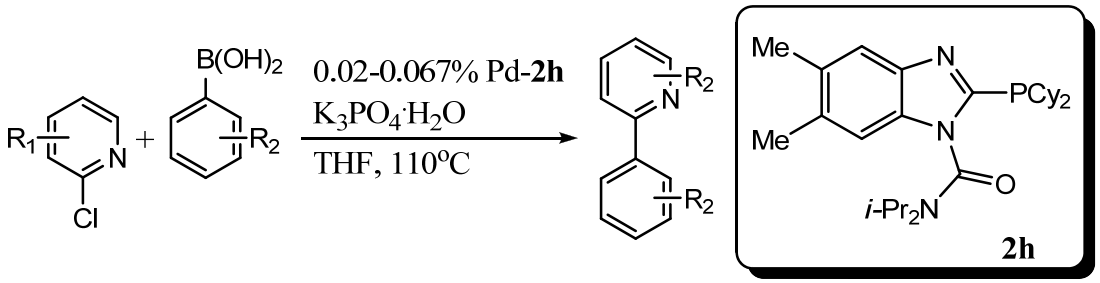
Apart from the study in deactivated substrates, the substrates which consisted of functional groups such as keto, aldehyde, ester, and nitriles were compatible under the reaction conditions. The catalyst loading of 0.01-0.05 mol% of Pd was achieved

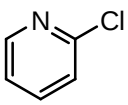
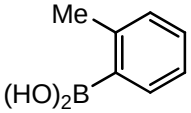
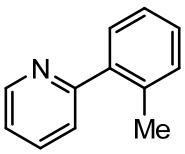
(Table 5, entries 7-12). Ligand **2h** could couple the aryl chlorides with activated functional groups and give excellent yields under very low catalyst loading. Generally, there was different reactivity of the substrates when the functional group at either *para*- or *meta*- position (Table 5, entries 8 and 9). Compared with entry 9, the keto group at *para*- position (entry 8) showed higher electron-withdrawing effect towards the C-Cl bond, resulting in higher catalytic activity.[21]

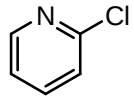
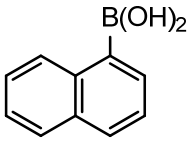
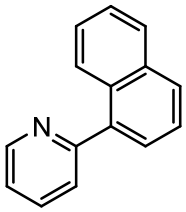
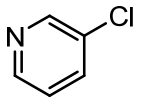
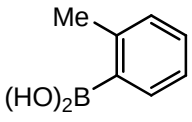
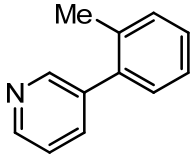
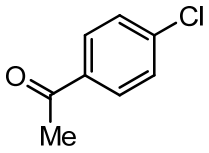
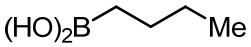
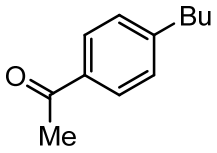
Among these activated aryl chlorides, electrophilic substrates having aldehyde and ester groups showed the highest reactivity and required the lowest catalyst loading, which could be down to 0.01 mol% Pd (Table 5, entries 10 and 11).

3.2.6. Suzuki-Miyaura coupling of Hetero-ArCl

Table 6: Palladium-Catalyzed Suzuki-Miyaura Coupling of Heteroaryl Chlorides with Aryl or Alkylboronic Acids[a]



entry	Het-ArCl	Ar'B(OH)$_2$	Product	mol% Pd	%yield[b]
1				0.02	82

2				0.05	84
3				0.067	80
4[c]				0.05	87

[a] Reaction conditions: Het-ArCl (1.0 mmole), Ar'B(OH)$_2$ (1.5 mmole), $K_3PO_4 \bullet H_2O$ (3.0 mmole), Pd(OAc)$_2$/L = 1:3, and THF (3 mL) were stirred for 24 h at 110°C under nitrogen. [b] Isolated yields. C Reaction conditions: ArCl (1.0 mmole), *n*-BuB(OH)$_2$ (2.0 mmole), $K_3PO_4 \bullet H_2O$ (3.0 mmole), Pd(OAc)$_2$/L = 1:3, and toluene (3 mL) were stirred for 24 h at 110°C under nitrogen.

Apart from functionalized aryl chlorides, the coupling of heteroaryl chlorides were also examined. The results showed that the heteroaryl chlorides were an effective substrates for Suzuki-Miyaura coupling with extremely low catalyst loading ranged from 0.02-0.067 mol% Pd (Table 5). The reactivity of the chloropyridine was mainly dependent on the position of chloro group on the pyridine ring. According to the catalyst loading, the reactivity of 2-chloropyridine was greatly higher than that of 3-chloropyridine. (Table 6, entries 1 and 3).

In addition, preliminary study in the coupling of alkylboronic acid with aryl chloride was successful (Table 6, entry 4). The optimized reaction conditions were modified by increasing the alkylboronic acid ratio to two equivalents and changing the solvent to toluene since the alkylboronic acid is more readily oxidized to stable alkane species

and toluene is an optimal solvent for the coupling due to solvent effects. Notably, it showed that this catalyst system could tolerate against β-H elimination with moderate catalyst loading.

3.3. Conclusion

A family of newly developed benzimidazole-based phosphine ligands has been reported. The ligands are highly tunable by changing the dialkylphosphine group and can be further fine-tuned by adding dimethyl group into the scaffold. The optimal ligand **2h** among the family is highly effective for Suzuki-Miyaura coupling of both activated and deactivated aryl chlorides and also heteroaryl chlorides. Some of them catalyzed the reaction under an extremely low catalyst loading which can be down to 0.01 mol% of palladium. Further exploration and versatility of this hemilabile P,O-type ligand will be attainable.

3.4 Experimental section

General Procedure for Suzuki-Miyaura Coupling of aryl chlorides: $Pd(OAc)_2$ (2.3 mg, 0.010 mmol) and ligand (0.030 mmol) were loaded into an oven-dried Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen for three times. Precomplexation was applied by adding freshly distilled THF into the tube. The solution was stirred for about 1 to 2 minutes until all the metal and ligand were dissolved in the solvent. Aryl chlorides (1.0 mmol), arylboronic acid (1.5 mmol), and $K_3PO_4 \bullet H_2O$ (3.0 mmol) were loaded into another Schlenk tube, and the system was further evacuated and flushed with nitrogen three times. The solvent THF (2.0 ml) was added, following the addition of catalyst dissolved in THF. The total volume of THF in the catalytic system is 3ml. The tube was stirred at room temperature for several minutes and then placed into a preheated oil bath (100 °C) for the time period as indicated in the tables. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and quenched with water and diluted with Ether. The organic layer was separated and the aqueous layer was washed with Ether twice. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

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Chapter 4

Summary

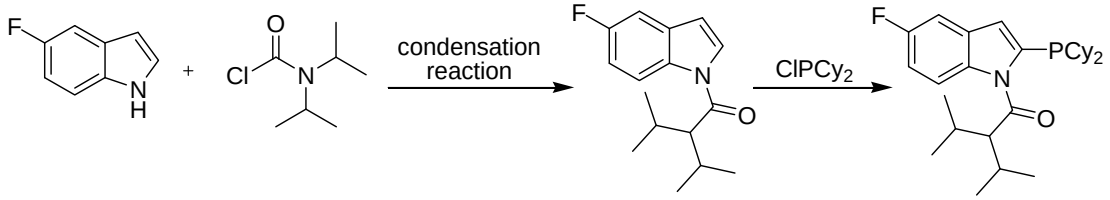
In conclusion, the addition of electron donating group on the scaffold could fine-tune and improve the overall reactivity of ligands. The possible reason was due to the enhancement of electron density on phosphorous atom, resulting in the faster rate of oxidative addition. But on the other hand, the addition of electron withdrawing group would inhibit the overall reactivity of ligands. The study of electronic effect towards the overall reactivity of phosphine ligands will contribute the further development and modification of related phosphine ligands.

Combined with the idea of previous research, the benzimidazole-based phosphine ligands' reactivity could be enhanced by adding two dimethyl groups into the scaffold. The optimal ligand was highly effective for Suzuki-Miyaura coupling of both activated and deactivated aryl chlorides and also heteroaryl chlorides. Some entries had an extremely low catalyst loading down to 0.01 mol% of palladium.

Appendix

Chapter 2: Supporting data of precursors and ligands

Synthesis of 1-(5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1a)



1a **2a**

General procedures for condensation reaction:

5-fluoro-1H-indole (4.05g, 30.0 mmol) was dissolved in 40ml THF in dropping funnel and added dropwisely to the 60ml THF solution contained 1.2 equiv NaH (60% in mineral oil, 1.44g, 36.0 mmol) at 0℃. NaH was washed with hexane (20 ml × 3) under N_2. The mixture stirred for 1 h at room temperature. After recooling to 0 °C 1.4 equiv N,N-diisopropylcarbamoylchloride (6.87g, 42.0 mmol) dissolved in 40 ml THF are added to the mixture dropwisely and the mixture is stirred at room temperature over night. Solvent was removed by vacuum. DCM 300 ml and water 100 ml was added to the mixture and the organic phase was separated. The remaining water phase was further extracted with 200 ml DCM twice. The combined organic phase was washed with brine and concentrated. The concentrated mixture was applied to 3 × 3cm silca pad and eluted with dichloromethane. The organic solvent was dried over Na_2SO_4 and evaporated in vacuum. The white powder of

1-(5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (4.10g, 52%) was obtained after column chromatography. Melting point: 63.2-65.1℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6.8Hz, 12H), 3.78-3.85 (m, 2H), 6.54-6.55 (m, 1H), 7.00-7.05 (m, 1H), 7.23-7.29 (m, 2H), 7.62-7.65 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.0, 48.5, 104.5, 105.5, 105.6, 105.8, 111.1, 111.4, 113.7, 126.6, 129.3, 129.4, 132.4, 152.3, 157.3, 159.7(Complex unresolved C-P splitting was observed); IR (cm^{-1}) 3131.32, 3110.65, 2994.49, 1971.33, 2935.55, 2875.94, 1674.75, 1619.67, 1515.39, 1434.22, 1376.11, 1337.46, 1264.53, 1157.10, 1080.37, 949.60, 876.67; MS (EI): *m/z* (relative intensity) 262 (M^+, 26), 204 (2), 176 (2), 162 (10), 135 (43), 128 (54), 107 (20), 86 (100), 70 (9); HRMS: calcd. for $C_{15}H_{19}N_2OFH^+$: 263.1560, found 263.1562.

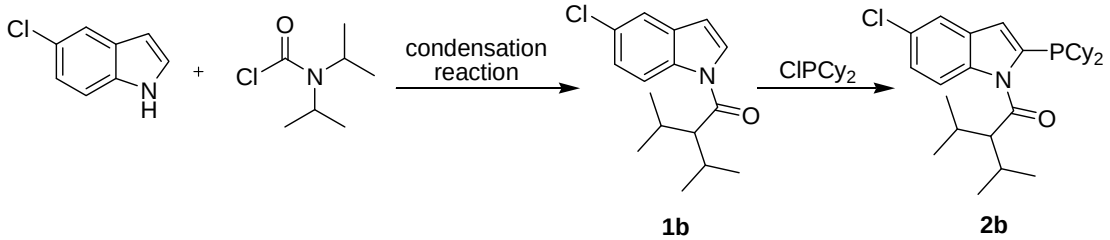
Synthesis of 1-(2-(dicyclohexylphosphino)-5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (2a)

General procedures for ligand synthesis:

1-(5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.32g, 5.0 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under nitrogen atmosphere. The solution was cooled to -78 °C in dry ice/acetone bath. Titrated n-BuLi (5.5 mmol) was added dropwise by syringe. After the reaction mixture was stirred for an hour at -78°C, chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) dissolved in 5 ml THF was added dropwise by syringe. The reaction was allowed to

warm to room temperature and stirred overnight. Solvent was removed under vacuum. After the solvent was removed under vacuum, the crude product was applied to column chromatography and the pure product was then dried under vacuum. White solid of title compound (1.28g, 56%) was obtained. Melting point: 157.3-159.4℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24-1.92 (m, 34H), 3.42 (bs, 2H), 6.70 (s, 1H), 6.95-7.00 (m, 1H), 7.21-7.28 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.5, 21.0, 26.2, 27.1, 29.9, 30.0, 30.1, 33.7, 104.8, 105.0, 105.1, 109.4, 109.5, 110.7, 110.9, 111.0, 128.1, 128.2, 133.4, 133.5, 136.7, 136.9, 151.3, 157.0, 159.3 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -21.56; IR (cm^{-1}) 2965.45, 2931.72, 1686.18, 1618.06, 1499.50, 1359.63, 1259.18, 1135.02, 1108.38, 1027.03, 848.36, 780.13; MS (EI): *m/z* (relative intensity) 458 (M^+, 10), 415 (53), 375 (100), 333 (27), 293 (7), 245 (17), 198 (17), 166 (40), 135 (8), 86 (13); HRMS: calcd. for $C_{27}H_{40}N_2OFPH^+$: 459.2941, found 459.2956.

Synthesis of 1-(5-chloro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1b)



1b **2b**

General procedures for the synthesis of precursor 1a were followed. 5-chloro-1H-indole (4.55g, 30.0 mmol), NaH (1.44g, 36.0 mmol), and

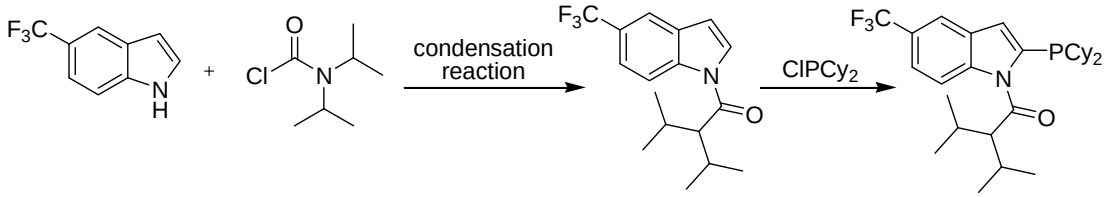
N,N-diisopropylcarbamoylchloride (6.87g, 42.0 mmol) were used to afford 1-(5-chloro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (5.86g, 70%) as white solid compound. Melting point: 100.14-102.7℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6.4Hz, 12H), 3.76-3.83 (m, 2H), 6.54 (t, *J* = 3.2 Hz, 1H), 7.22-7.28 (m, 2H), 7.58-7.63 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.0, 48.6, 104.0, 104.1, 113.7, 113.8, 120.0, 120.1, 123.2, 123.3, 126.3, 126.4, 126.8, 129.9, 134.2, 152.0(Complex unresolved C-P splitting was observed); IR (cm^{-1}) 3004.42, 2971.01, 2929.10, 1677.15, 1435.52, 1377.49, 1300.77, 1265.20, 1157.52, 1124.16, 1064.72, 1013.29, 898.52; MS (EI): *m/z* (relative intensity) 278 (M^+, 25), 178 (8), 151 (33), 128 (63), 116 (8), 86 (100), 70 (8); HRMS: calcd. for $C_{15}H_{19}N_2OClH^+$: 279.1264, found 279.1267.

Synthesis of 1-(5-chloro-2-(dicyclohexylphosphino)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (2b)

General procedures for the synthesis of ligand 2a were followed. 1-(5-chloro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.40g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) were used to afford 1-(5-chloro-2-(dicyclohexylphosphino)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.87g, 79%) as white solid compound. Melting point: 169.1-171.7℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24-1.99 (m, 34H), 3.46-3.51 (m, 2H),

6.68 (s, 1H), 7.15-7.30 (2H), 7.59-7.64 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.6, 21.1, 26.2, 27.1, 29.9, 30.0, 33.7, 109.0, 111.1, 119.6, 122.7, 126.0, 128.8, 135.1, 136.5, 136.7, 151.0(Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -21.64; IR (cm^{-1}) 2989.71, 2928.64, 2846.80, 1696.66, 1488.94, 1435.63, 1369.74, 1156.60, 1062.24, 1000.20, 887.15, 783.41, 710.60, 650.26, 552.20; MS (EI): *m/z* (relative intensity) 474 (M^+, 10), 431 (45), 391 (100), 349 (23), 309 (8), 276 (8), 261 (18), 225 (16), 198 (27), 182 (36); HRMS: calcd. for $C_{27}H_{40}N_2OClPH^+$: 475.2645, found 459.2651.

Synthesis of 1-(5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1c)



1c **2c**

General procedures for the synthesis of precursor 1a were followed. 5-(trifluoromethyl)-1H-indole (1.35g, 7.5 mmol), NaH (0.33g, 8.25 mmol), and N,N-diisopropylcarbamoylchloride (1.48g, 9.0 mmol) were used to afford 1-(5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.99g, 85%) as orange solid compound. Melting point: 77.4-78.1℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, *J* = 6.9Hz, 12H), 3.79-3.82 (m, 2H), 6.69 (d, *J* = 3.3Hz, 1H), 7.31 (t, *J* =

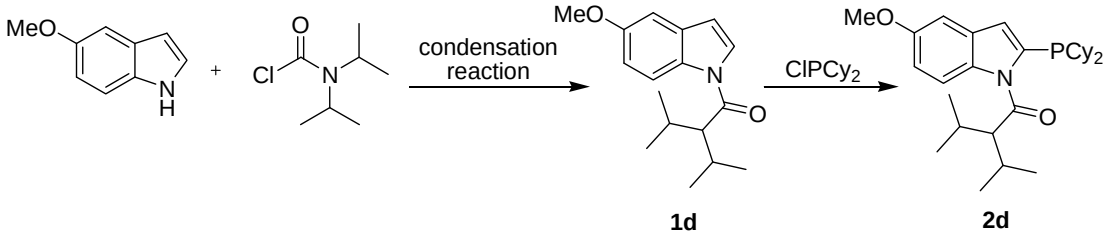
5.5Hz, 1H), 7.54 (d, *J* = 7.7Hz, 1H), 7.77 (d, *J* = 8.7Hz, 1H), 7.94 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.1, 48.7, 105.2, 113.0, 118.4, 118.5, 119.9, 123.6, 123.7, 123.9, 126.4, 126.8, 128.3, 137.3, 139.6, 151.9 (Complex unresolved C-P splitting was observed); IR (cm^{-1}) 3003.73, 2978.69, 1681.65, 1527.18, 1432.48, 1263.69, 1217.01, 1108.12, 1014.71, 886.35, 748.95, 611.16; MS (EI): *m/z* (relative intensity) 312 (M^+, 18), 293 (2), 254 (2), 226 (2), 212 (9), 185 (41), 166 (10), 158 (5), 145 (2), 137 (5), 128 (73), 86 (100); HRMS: calcd. for $C_{16}H_{19}N_2OF_3H^+$: 313.1528, found 313.1531.

Synthesis of 1-(2-(dicyclohexylphosphino)-5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (2c)

General procedures for the synthesis of ligand 2a were followed. 1-(5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.56g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) were used to afford 1-(2-(dicyclohexylphosphino)-5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.27g, 50%) as white solid compound. Melting point: 191.1-192.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91-2.20 (m, 34H), 3.31-3.61 (m, 2H), 6.85 (s, 1H), 7.39-7.48 (m, 2H), 7.95 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.3, 20.7, 20.8, 21.0, 26.2, 26.5, 26.8, 27.2, 27.3, 27.4, 28.9, 29.0, 30.1, 30.2, 30.4, 33.7, 110.3, 110.5, 118.1, 118.2, 119.1, 122.7, 123.0, 123.8, 126.5, 127.2, 137.4, 137.6, 138.0, 150.8 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz,

$CDCl_3$) δ -21.79; IR (cm^{-1}) 2977.00, 2958.31, 2927.14, 2873.91, 2846.83, 1696.73, 1471.67, 1445.82, 1314.46, 1265.22, 1205.15, 1113.02, 1027.84, 999.35, 896.09, 854.49, 793.66, 649.30; MS (EI): *m/z* (relative intensity) 508 (M^+, 7), 489 (6), 465 (74), 425 (100), 383 (27), 343 (7), 315 (6), 301 (22), 259 (20), 241 (6), 216 (30), 198 (29), 166 (7), 117 (6), 86 (9), 55 (10); HRMS: calcd. for $C_{28}H_{40}N_2OF_3PH^+$: 509.2909, found 509.2914.

Synthesis of 2-isopropyl-1-(5-methoxy-1H-indol-1-yl)-3-methylbutan-1-one (1d)



1d **2d**

General procedures for the synthesis of precursor 1a were followed. 5-methoxy-1H-indole (4.42g, 30.0 mmol), NaH (1.44g, 36.0 mmol), and N,N-diisopropylcarbamoylchloride (6.87g, 42.0 mmol) were used to afford 2-isopropyl-1-(5-methoxy-1H-indol-1-yl)-3-methylbutan-1-one (7.23g, 88%) as white solid compound. Melting point: 68.7-69.3℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, *J* = 6.6Hz, 12H), 3.82-3.88 (m, 2H), 3.89 (s, 3H), 6.53 (d, *J* = 3.6Hz, 1H), 6.93-6.96 (m, 1H), 7.09 (d, *J* = 2.5Hz, 1H), 7.19 (d, *J* = 3.5Hz, 1H), 7.62 (d, *J* = 8.9Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.9, 21.0, 48.3, 55.5, 102.5, 104.4, 112.7, 113.5, 125.6,

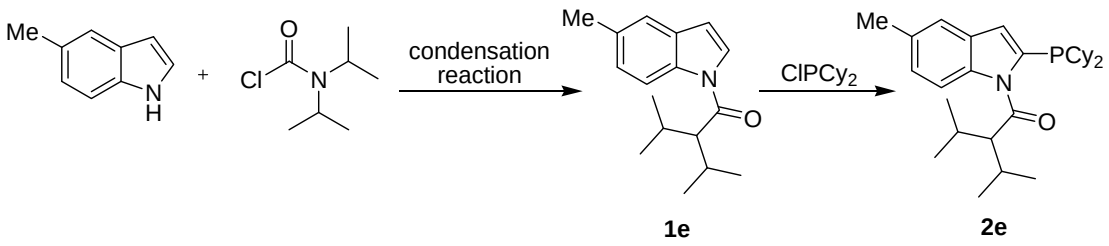
129.4, 130.8, 152.5, 154.9, 155.0 (Complex unresolved C-P splitting was observed); IR (cm^{-1}) 3002.71, 2968.38, 1674.96, 1618.62, 1507.67, 1434.68, 1313.60, 1273.83, 1213.67, 1113.93, 1077.73, 859.84, 722.37, 603.68; MS (EI): *m/z* (relative intensity) 274 (M^+, 67), 216 (2), 188 (2), 174 (17), 159 (2), 147 (17), 135 (38), 128 (54), 117 (5), 104 (17), 86 (100), 76 (8); HRMS: calcd. for $C_{16}H_{22}N_2O_2H^+$: 275.1760, found 275.1770.

Synthesis of 1-(2-(dicyclohexylphosphino)-5-methoxy-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (2d)

General procedures for the synthesis of ligand 2a were followed. 2-isopropyl-1-(5-methoxy-1H-indol-1-yl)-3-methylbutan-1-one (1.37g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) were used to afford 1-(2-(dicyclohexylphosphino)-5-methoxy-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.62g, 69%) as white solid compound. Melting point: 142.3-142.9℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24-1.92 (m, 34H), 3.43-3.52 (m, 2H), 3.87 (d, *J* = 10.7 Hz, 1H), 6.67 (s,1H), 6.89 (d, *J* = 6.6 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.23 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.3, 20.5, 20.7, 20.8, 26.3, 26.5, 27.1, 27.2, 28.9, 29.0, 29.2, 29.8, 30.0, 30.1, 33.8, 55.6, 101.4, 109.3, 109.4, 111.1, 113.0, 128.3, 132.2, 135.1, 135.3, 151.7, 154.6 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -21.84; IR

(cm^{-1}) 2995.22, 2929.82, 2851.00, 1685.57, 1618.68, 1501.43, 1470.83, 1427.35, 1370.59, 1361.22, 1272.26, 1226.83, 1163.70, 1119.92, 1002.58, 852.63, 830.40, 792.24; MS (EI): *m/z* (relative intensity) 470 (M^+, 9), 427 (38), 387 (100), 370 (2), 345 (26), 305 (6), 272 (34), 257 (24), 221 (8), 203 (6), 178 (51), 147 (16), 112 (8), 86 (16), 55 (14); HRMS: calcd. for $C_{28}H_{43}N_2O_2PH^+$: 471.3140, found 471.3150.

Synthesis of 2-isopropyl-3-methyl-1-(5-methyl-1H-indol-1-yl)butan-1-one (1e)



1e **2e**

General procedures for the synthesis of precursor 1a were followed. 5-methyl-1H-indole (3.93g, 30.0 mmol), NaH (1.44g, 36.0 mmol), and N,N-diisopropylcarbamoylchloride (6.87g, 42.0 mmol) were used to afford 2-isopropyl-3-methyl-1-(5-methyl-1H-indol-1-yl)butan-1-one (5.34g, 69%) as orange solid compound. Melting point: 75.7-77.1℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, *J* = 6.8Hz, 12H), 2.49 (d, *J* = 9.3Hz, 3H), 3.81-3.86 (m, 2H), 6.52 (d, *J* = 3.4Hz, 1H), 7.11-7.19 (m, 2H), 7.42 (s, 1H), 7.59 (d, *J* = 8.4Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.0, 21.2, 21.3, 48.4, 104.2, 112.4, 120.4, 124.6, 125.2, 129.1, 130.5, 134.1, 152.7 (Complex unresolved C-P splitting was observed); IR (cm^{-1}) 2971.14, 2929.45,

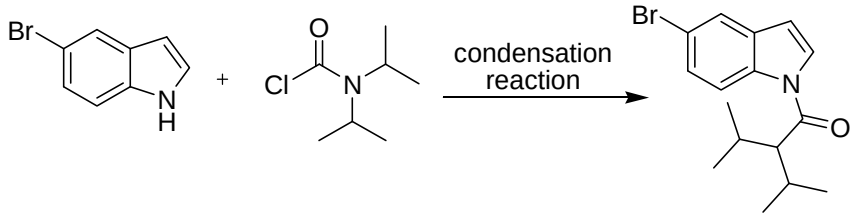
1671.10, 1430.03, 1375.29, 1325.89, 1215.27, 1157.23, 1013.60, 897.36, 721.71, 649.78, 612.28, 546.84, 514.97, 468.57, 429.99; MS (EI): *m/z* (relative intensity) 258 (M^+, 58), 200 (2), 185 (1), 172 (2), 158 (18), 143 (2), 130 (63), 117 (2), 103 (11), 86 (100), 77 (11); HRMS: calcd. for $C_{16}H_{22}N_2OH^+$: 259.1810, found 259.1809.

Synthesis of 1-(2-(dicyclohexylphosphino)-5-methyl-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (2e)

General procedures for the synthesis of ligand 2a were followed. 2-isopropyl-3-methyl-1-(5-methyl-1H-indol-1-yl)butan-1-one (1.29g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33ml, 6.0 mmol) were used to afford 1-(2-(dicyclohexylphosphino)-5-methyl-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.52g, 67%) as white solid compound. Melting point: 162.3 -163.1℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.76 (m, 30H), 1.95 (m, 2H), 2.31-2.33 (m, 2H), 2.47 (s, 3H), 3.48-3.53 (m, 2H), 6.69 (s, 1H), 7.04 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 8.4Hz, 1H), 7.40 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.5, 20.8, 21.2, 21.3, 25.6, 26.0, 26.3, 26.4, 26.7, 30.6, 30.8, 37.1, 37.4, 37.5, 37.8, 48.5, 48.7, 108.7, 108.8, 110.0, 119.8, 119.9, 120.2, 124.1, 128.2, 129.6, 135.0, 135.1, 137.5, 137.7, 151.8 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -25.20; IR (cm^{-1}) 2975.02, 2923.11, 2846.57, 1685.16, 1430.89, 1311.37, 1267.48, 1206.19, 1159.83, 1133.40, 1114.15, 1026.36, 1000.90, 866.46, 828.54, 794.85; MS

(EI): *m/z* (relative intensity) 454 (M^+, 7), 411 (51), 371 (100), 354 (2), 342 (5), 329 (29), 289 (6), 256 (32), 241 (40), 205 (15), 187 (6), 162 (71), 131 (25), 112 (6), 86 (25); HRMS: calcd. for $C_{28}H_{43}N_2OPH^+$: 455.3191, found 455.3208.

Synthesis of 1-(5-bromo-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1f)

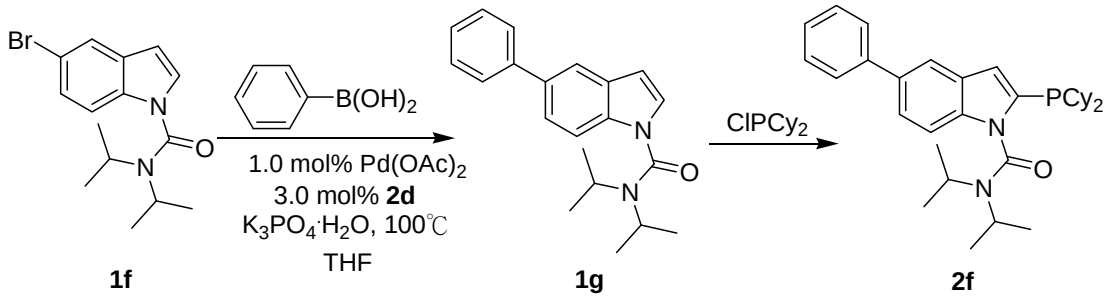


1f

General procedures for the synthesis of precursor 1a were followed. 5-bromo-1H-indole (3.84g, 20.0 mmol), NaH (0.88g, 22.0 mmol), and N,N-diisopropylcarbamoylchloride (3.94g, 24.0 mmol) were used to afford 1-(5-bromo-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (5.09g, 79%) as white solid compound. Melting point: 95.1-96.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, *J* = 6.7Hz, 12H), 3.79-3.84 (m, 2H), 6.54 (d, *J* = 3.9Hz, 1H), 7.21 (d, *J* = 3.8Hz, 1H), 7.38 (d, *J* = 6.9Hz, 1H), 7.58 (d, *J* = 8.7Hz, 1H),7.76 (d, *J* = 1.8Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.9, 48.5, 103.9, 114.2, 114.3, 123.2, 125.8, 126.2, 130.4, 134.5, 151.9 (Complex unresolved C-P splitting was observed); IR (cm^{-1}) 3004.69, 2928.17, 1667.24, 1428.10, 1323.96, 1214.03, 1157.37, 1084.06, 896.29, 818.94, 717.24, 687.95, 636.27, 576.76, 470.49, 428.01; MS (EI): *m/z* (relative intensity) 322 (M^+, 20),

264 (1), 238 (1), 224 (4), 195 (17), 168 (2), 157 (2), 143 (4), 128 (82), 115 (17), 86 (100), 70 (9); HRMS: calcd. for $C_{15}H_{19}N_2OBrH^+$: 323.0759, found 323.0769.

Synthesis of N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide (1g)



Precursor **1g** is synthesized by the coupling between precursor **1f** and phenyl boronic acid through Suzuki-Miyaura Coupling. 1-(5-bromo-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one (1.61g, 5.0 mmol), phenyl boronic acid (7.5 mmol), and $K_3PO_4 \cdot H_2O$ (3.42g, 15.0 mmol), with 1.0 mol% $Pd(OAc)_2$, 3.0 mol% ligand **2d** and 15ml THF under 100℃ were used to afford N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide (2.12g, 82%) as white solid compound. Melting point: 95.1-96.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.5Hz, 12H), 3.86-3.89 (m, 2H), 6.67 (s, 1H), 7.27 (t, *J* = 1.0Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.3Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 7.7Hz, 2H), 7.79 (d, *J* = 8.6Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.1, 48.2, 104.9, 112.6, 112.9, 118.7, 119.1, 122.5, 122.7, 125.5, 126.4, 126.8, 127.1, 127.4, 128.2, 128.3, 129.3, 134.6, 135.3, 139.5, 141.8, 152.3, 154.2 (Complex unresolved C-P splitting was observed); MS (EI): *m/z* (relative

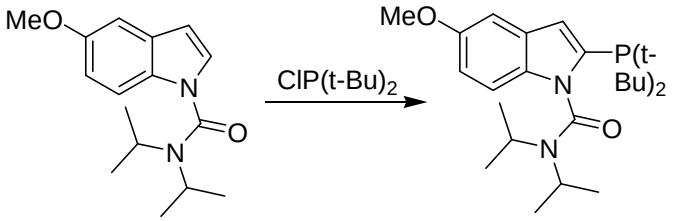
intensity) 320 (M^+, 49), 234 (2), 220 (10), 204 (2), 193 (42), 177 (3), 165 (24), 152 (3), 139 (5), 128 (66), 115 (3), 86 (100), 70 (3); HRMS: calcd. for $C_{21}H_{24}N_2OH^+$: 321.1967, found 321.1970.

Synthesis of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide (2f)

General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide (4.89g, 15.0 mmol), n-BuLi (16.5 mmol), and chlorodicyclohexylphosphine (3.99ml, 18.0 mmol) were used to afford 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide (4.40g, 64%) as white solid compound. Melting point: 188.1-189.4℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.94 (m, 34H), 3.51 (m, 2H), 6.80 (s, 1H), 7.33-7.39 (m, 2H), 7.47 (t, *J* = 6.3Hz, 3H), 7.67 (d, *J* = 7.7Hz, 2H), 7.83 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.7, 21.0, 26.3, 27.2, 30.0, 30.1, 33.9, 110.1, 110.5, 118.7, 122.5, 126.3, 127.2, 128.4, 128.6, 134.1, 135.6, 135.8, 136.4, 142.2, 151.5 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -21.90; IR (cm^{-1}) 2923.76, 2846.01, 1692.87, 1430.49, 1369.69, 1311.84, 1263.85, 1025.57, 763.24, 699.99; MS (EI): *m/z* (relative intensity) 516 (M^+, 8), 473 (42), 433 (100), 391 (22), 351 (5), 318 (32), 303 (30), 267 (11), 249 (7), 224 (48), 193 (26), 165 (7), 112 (9), 86 (16), 55 (20); HRMS: calcd. for $C_{33}H_{45}N_2OPH^+$: 517.3348, found

517.3355.

Synthesis of 2-(di-tert-butylphosphino)-N,N-diisopropyl-5-methoxy-1 H-indole-1-carboxamide (2g)

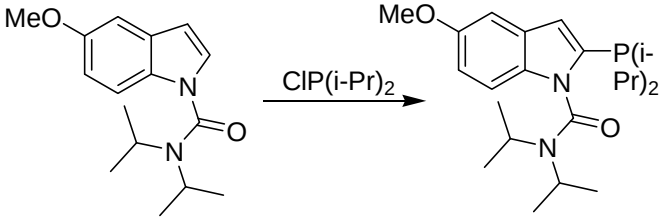


1d **2g**

General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide (1.37g, 5.0 mmol), n-BuLi (5.5 mmol), and di-tert-butylchlorophosphine (1.14ml, 6.0 mmol) were used to afford 2-(di-tert-butylphosphino)-N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide (1.49g, 71%) as white solid compound. Melting point: 128.6-129.7℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.70 (m, 30H), 3.69 (m, 2H), 3.87 (s, 3H), 6.87-6.95 (m, 2H), 7.08 (d, *J* = 2.5Hz, 1H), 7.18-7.22 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.8, 21.2, 30.5, 30.6, 32.8, 33.0, 48.5, 55.6, 101.6, 102.7, 104.5, 111.3, 111.7, 112.9, 113.3, 113.6, 125.7, 128.6, 129.5, 130.9, 132.2, 132.3, 136.0, 136.2, 151.2, 154.6, 155.1 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ 9.43; IR (cm^{-1}) 2978.42, 2950.38, 2861.30, 1688.48, 1615.43, 1501.92, 1433.35, 1418.05, 1376.40, 1312.08, 1219.78, 1199.58, 1117.92, 1026.89, 869.22, 833.52, 800.47; MS (EI): *m/z* (relative intensity) 417 (M^+, 1), 375 (2), 361 (100), 333 (2), 319

(9), 305 (5), 277 (5), 263 (19), 248 (2), 234 (5), 221 (11), 178 (17), 147 (5), 86 (5), 57 (7); HRMS: calcd. for $C_{24}H_{39}N_2O_2PH^+$: 419.2827, found 419.2840.

Synthesis of N,N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide (2h)

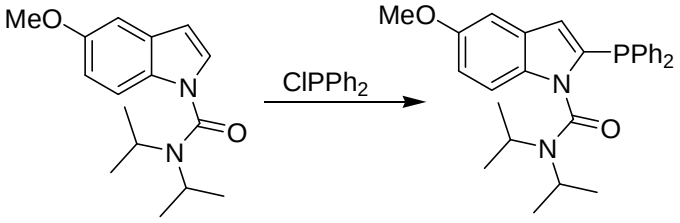


1d **2h**

General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide (1.37g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiisopropylphosphine (0.96ml, 6.0 mmol) were used to afford N,N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide (1.47g, 75%) as white solid compound. Melting point: 110.1-111.8℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.60 (m, 26H), 2.18 (s, 2H), 3.45-3.51 (m, 2H), 3.87 (s, 3H), 6.67 (d, *J* = 0.4Hz, 1H), 6.87-6.90 (m, 1H), 7.06 (d, *J* = 2.4Hz, 1H), 7.21 (d, *J* = 8.8Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 19.7, 19.9, 20.6, 24.1, 55.7, 101.6, 109.3, 109.4, 111.1, 113.2, 128.3, 132.2, 132.3, 135.4, 135.6, 151.2, 154.6 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -13.36; IR (cm^{-1}) 2993.22, 2921.52, 2863.83, 1682.15, 1612.97, 1502.85, 1435.52, 1378.43, 1351.33, 1319.53, 1223.68, 1199.91, 1162.23, 1063.12, 1026.86, 872.68, 854.51,

794.90, 607.65; MS (EI): *m/z* (relative intensity) 390 (M^+, 7), 347 (100), 305 (95), 290 (7), 279 (8), 263 (10), 220 (15), 203 (7), 189 (7), 178 (35), 147 (14), 135 (8), 86 (14); HRMS: calcd. for $C_{22}H_{35}N_2O_2PH^+$: 391.2514, found 391.2499.

Synthesis of N,N-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide (2i)



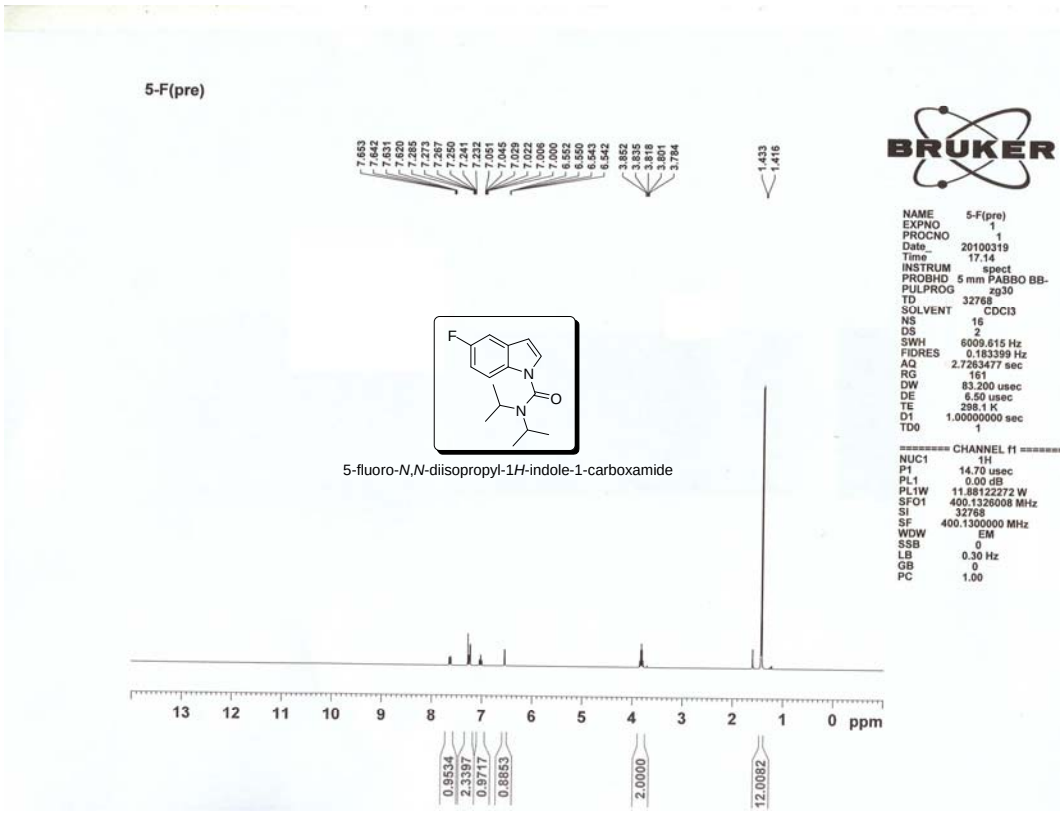
1d **2i**

General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-5-methoxy-1H-indole-1-carboxamide (1.37g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiphenylphosphine (1.11ml, 6.0 mmol) were used to afford N,N-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide (1.49g, 65%) as white solid compound. Melting point: 186.1-187.4℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.4Hz, 12H), 3.50-3.57 (m, 2H), 3.83 (s, 3H), 6.23 (s, 1H), 6.89-6.91 (m, 1H), 6.97 (d, *J* = 2.4Hz, 1H), 7.23 (d, *J* = 8.8Hz, 1H), 7.34-7.45 (m, 10H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.6, 20.7, 21.2, 48.5, 48.8, 55.6, 55.7, 102.0, 111.3, 112.4, 113.6, 125.7, 128.3, 128.4, 128.5, 128.8, 133.1, 133.2, 133.4, 133.6, 135.9, 136.0, 136.7, 136.8, 151.2, 154.8 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -27.76; IR (cm^{-1}) 2958.58, 1686.05,

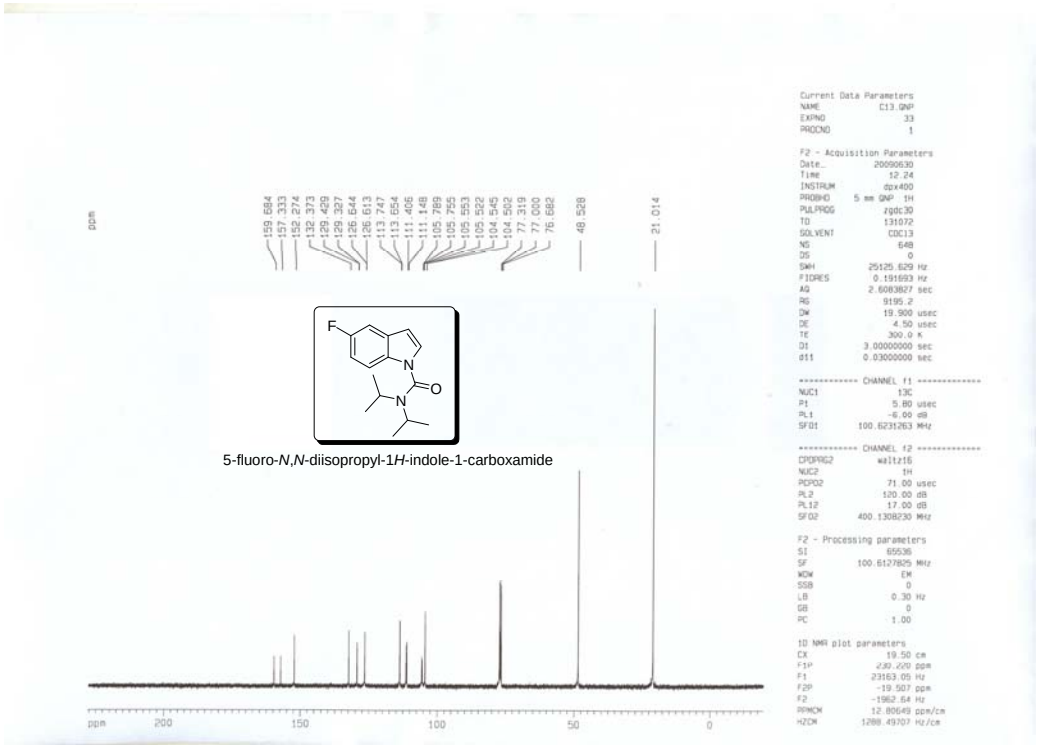
1616.61, 1471.19, 1432.60, 1369.15, 1318.06, 1165.12, 1118.11, 1061.10, 944.05, 910.07, 878.94, 742.26, 692.79, 610.08, 545.56, 501.42, 425.19; MS (EI): *m/z* (relative intensity) 458 (M^+, 7), 415 (27), 373 (100), 360 (7), 347 (27), 331 (13), 314 (3), 299 (3), 286 (5), 272 (63), 257 (25), 238 (5), 223 (9), 209 (16), 183 (16), 86 (28); HRMS: calcd. for $C_{28}H_{31}N_2O_2PH^+$: 459.2201, found 459.2216.

Chapter 2: NMR spectrum and mass spectrum of precursors and ligands

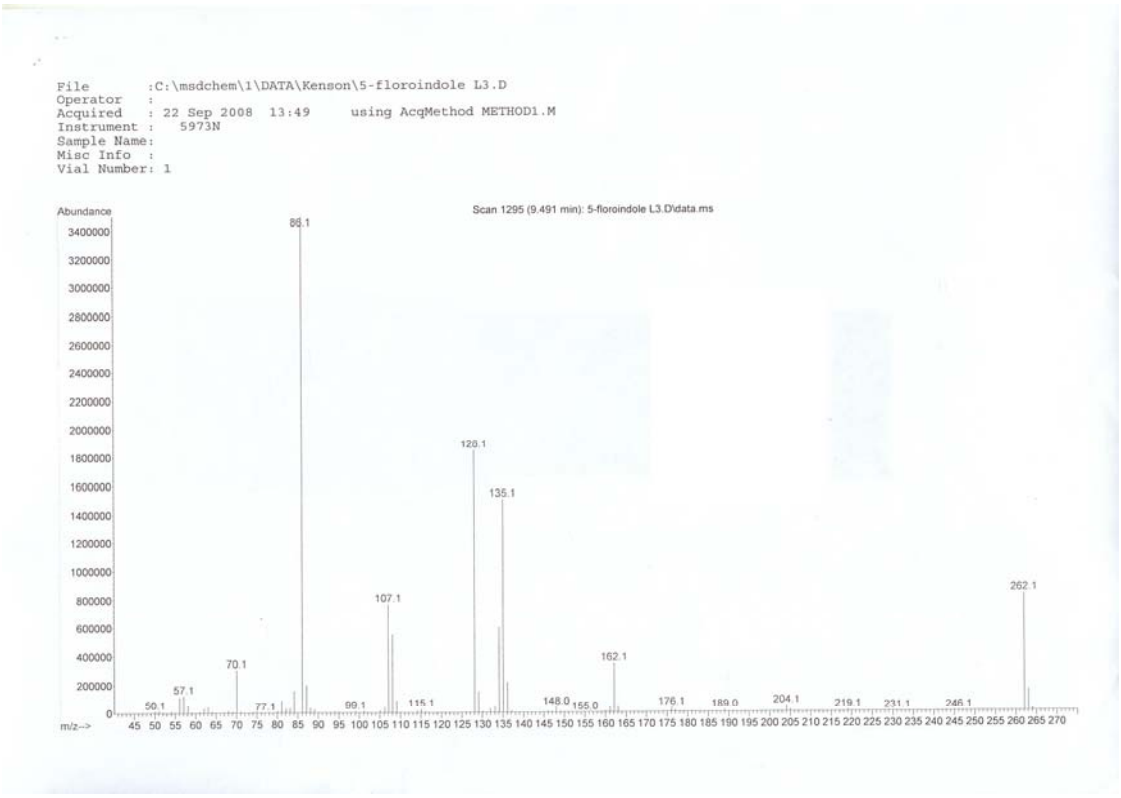
^{1}H NMR of 5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



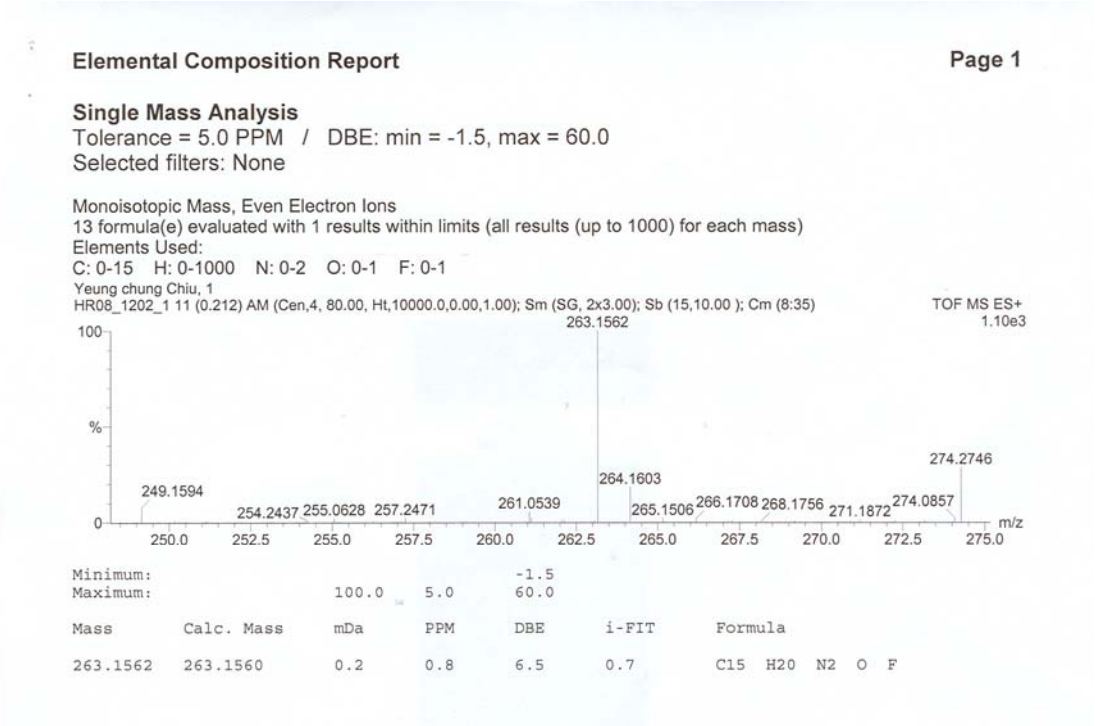
^{13}C NMR of 5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



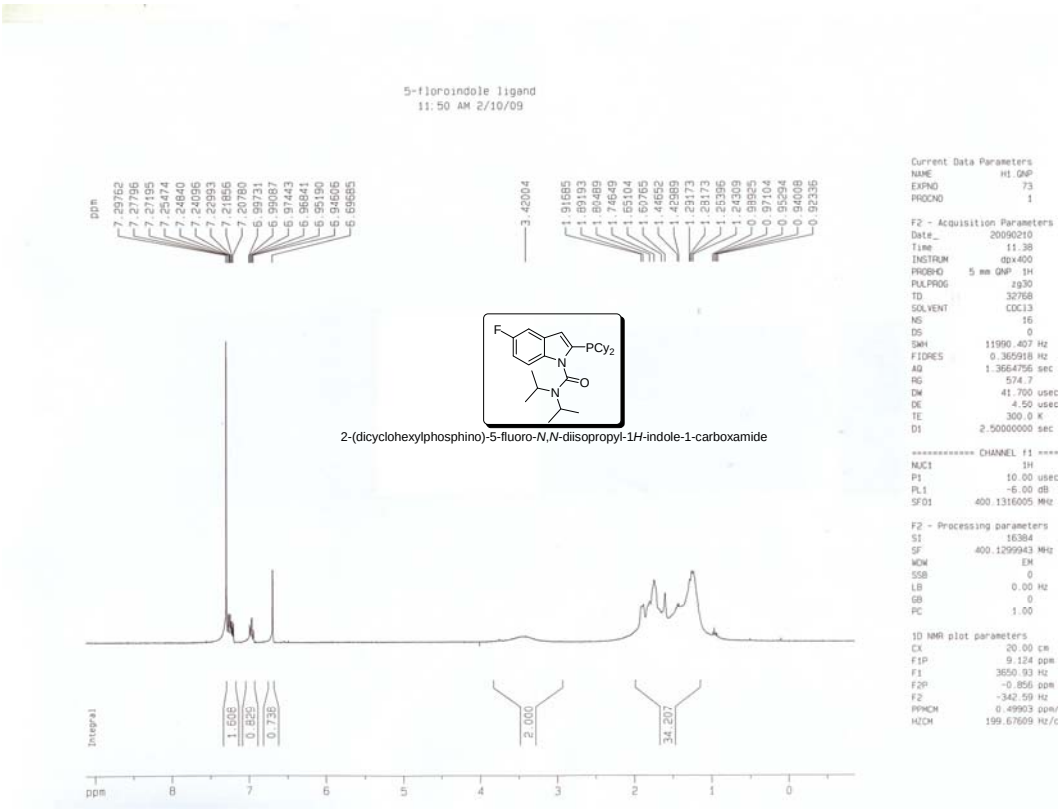
Mass spectrum of 5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



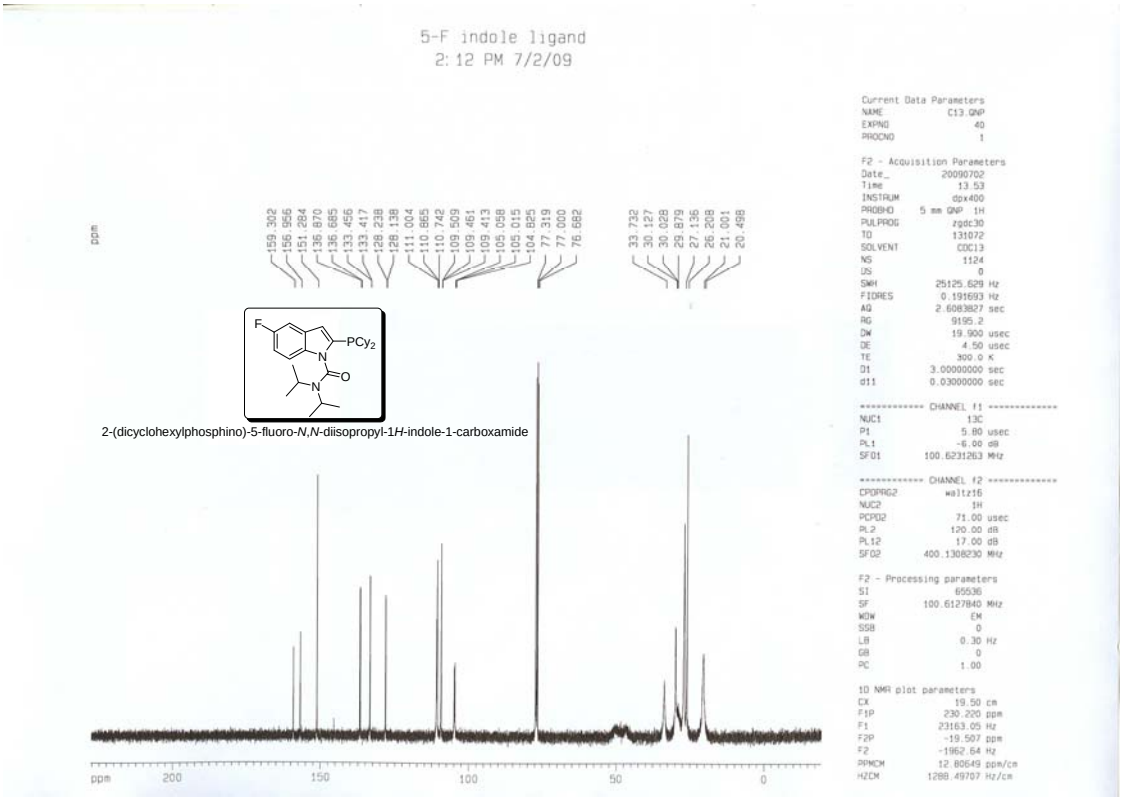
High resolution mass spectrum of 5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



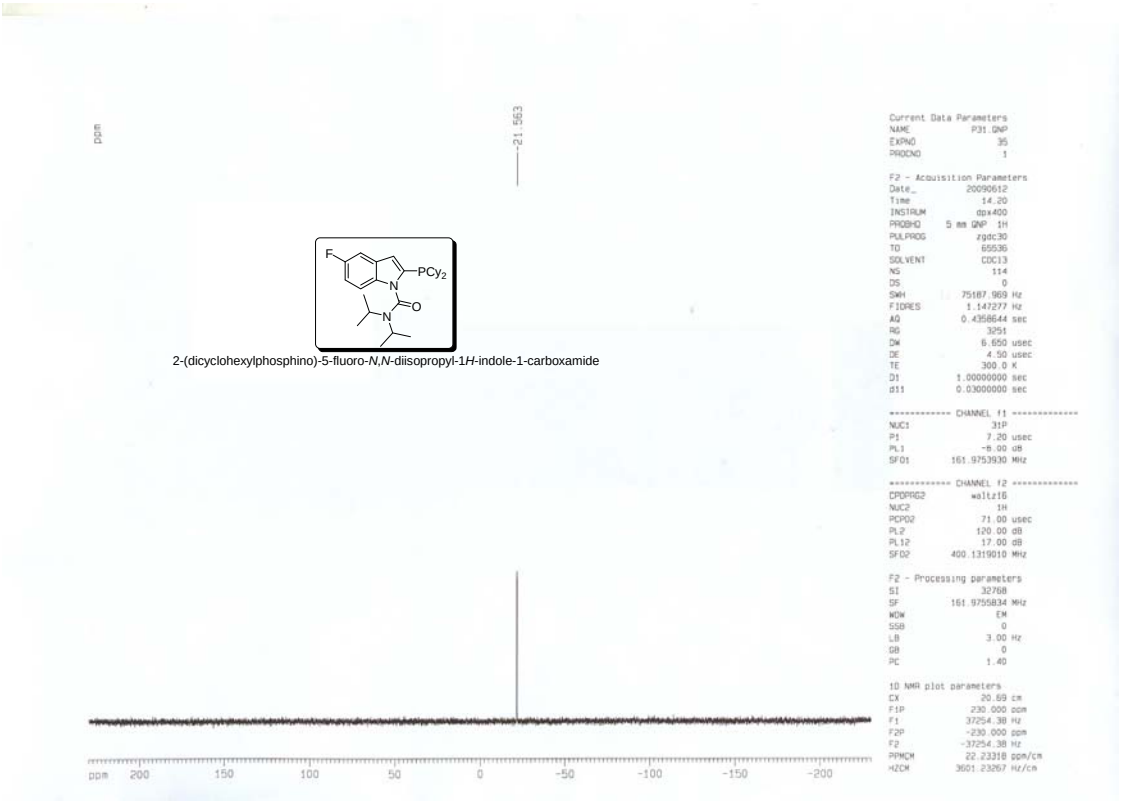
^{1}H NMR of 2-(dicyclohexylphosphino)-5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



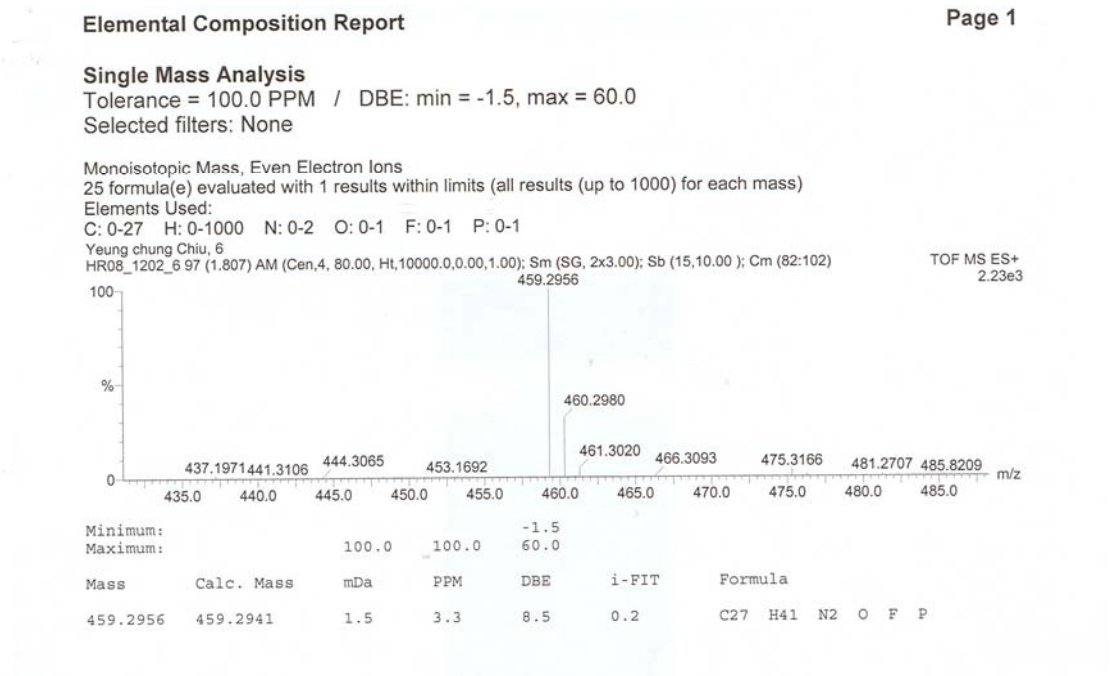
^{13}C NMR of 2-(dicyclohexylphosphino)-5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



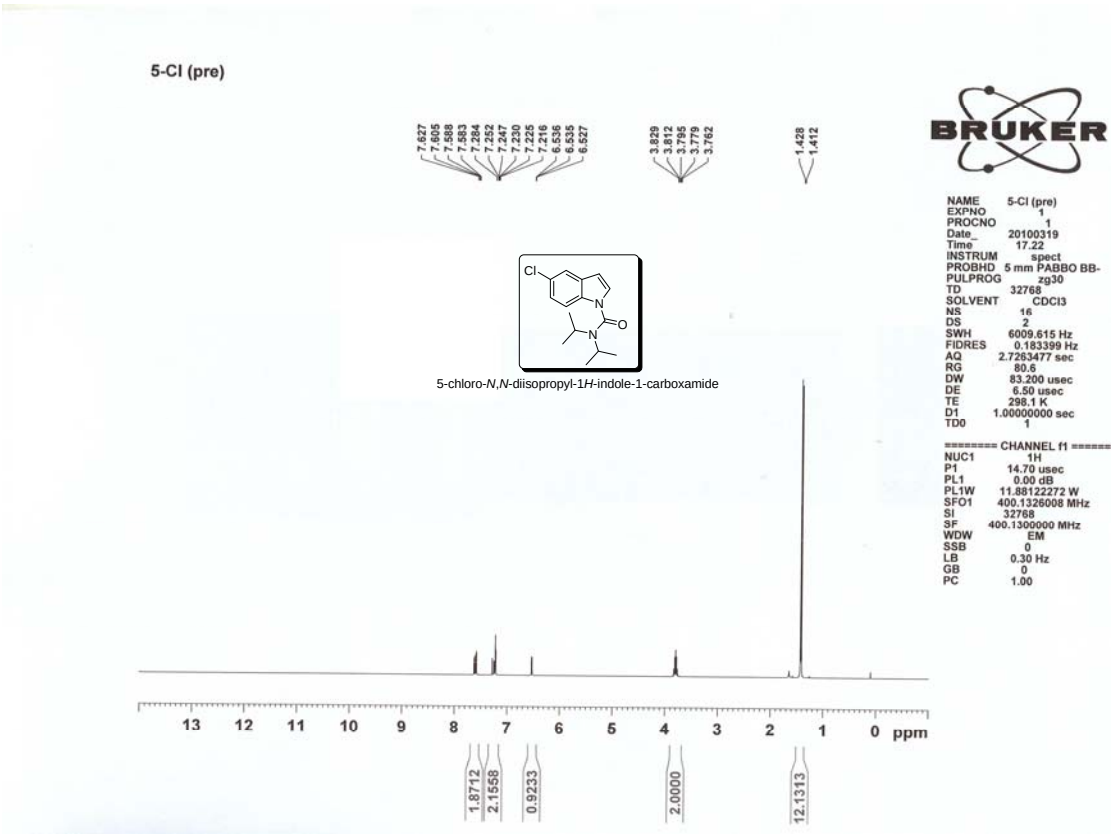
^{31}P NMR of 2-(dicyclohexylphosphino)-5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



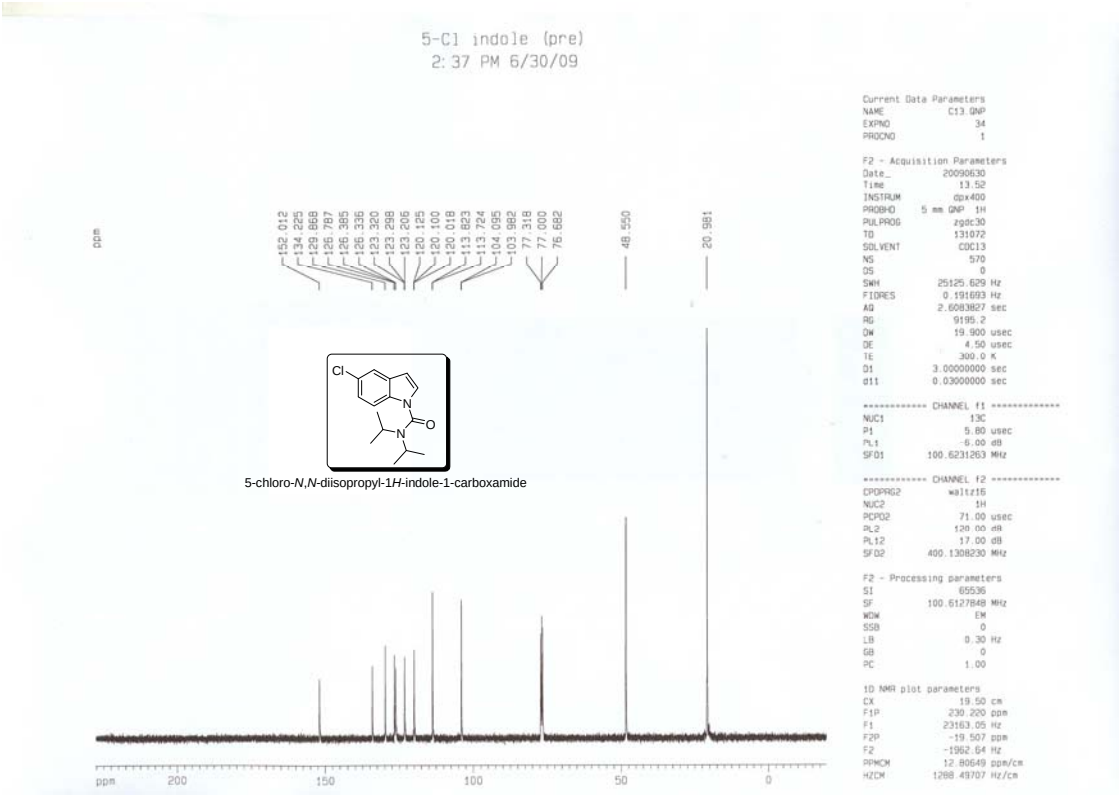
High resolution mass spectrum of 2-(dicyclohexylphosphino)-5-fluoro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



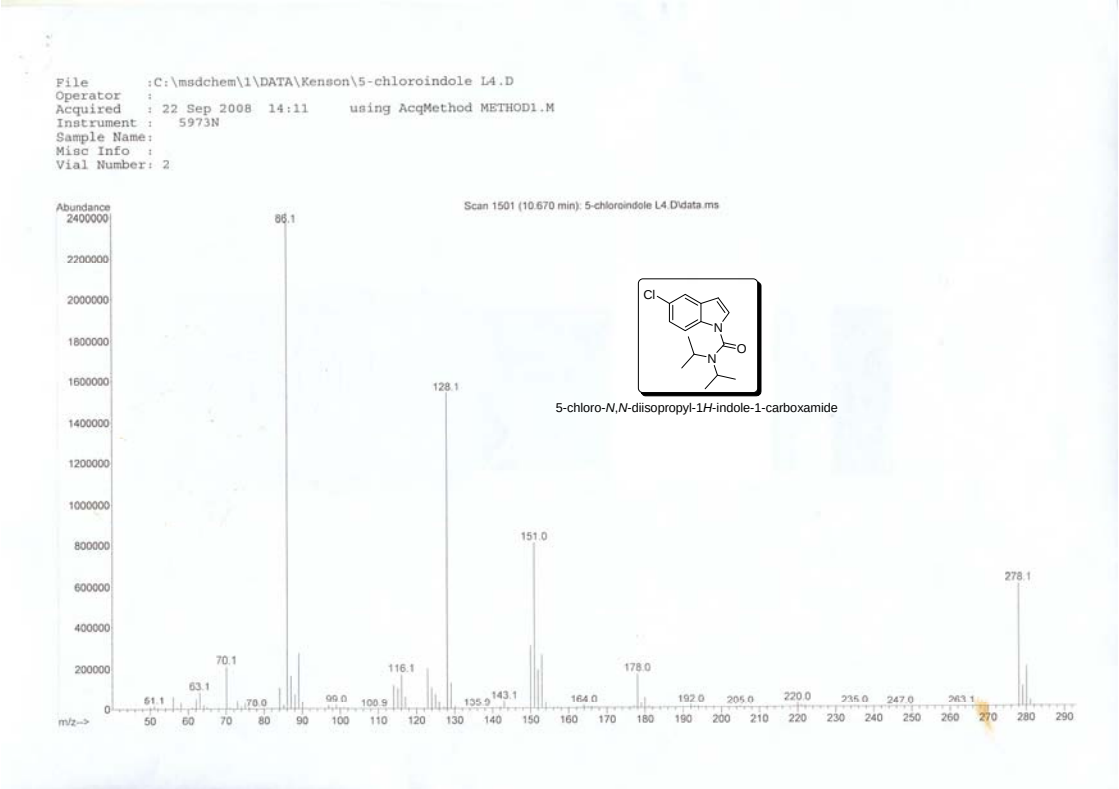
^{1}H NMR of 5-chloro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



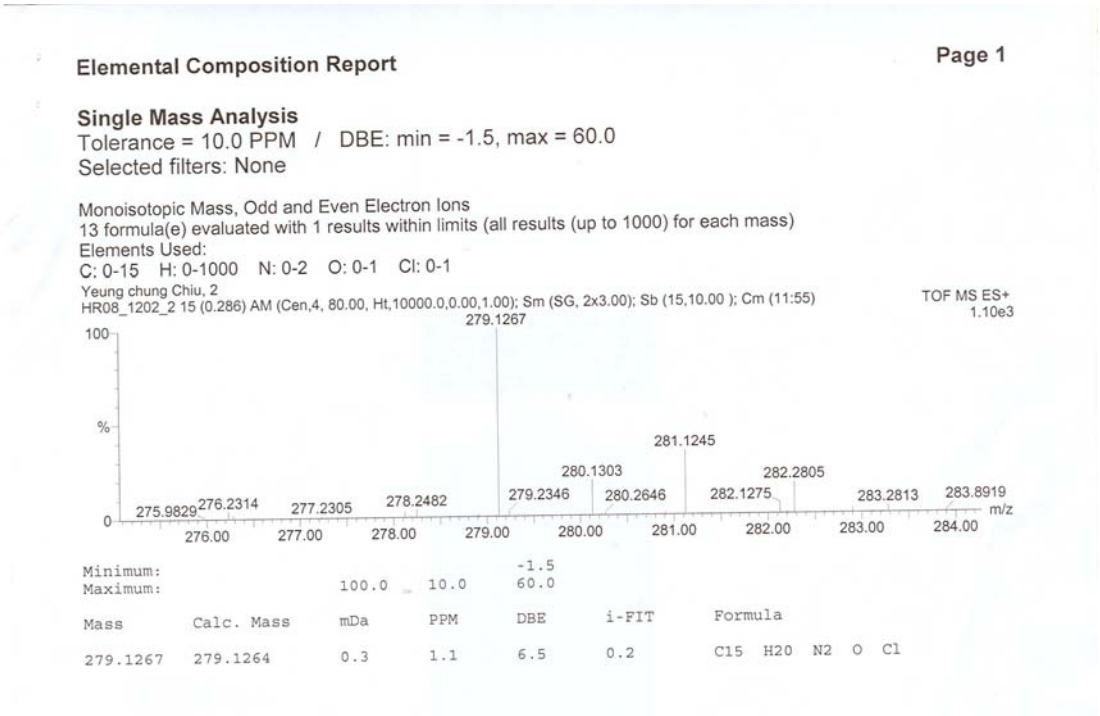
^{13}C NMR of 5-chloro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



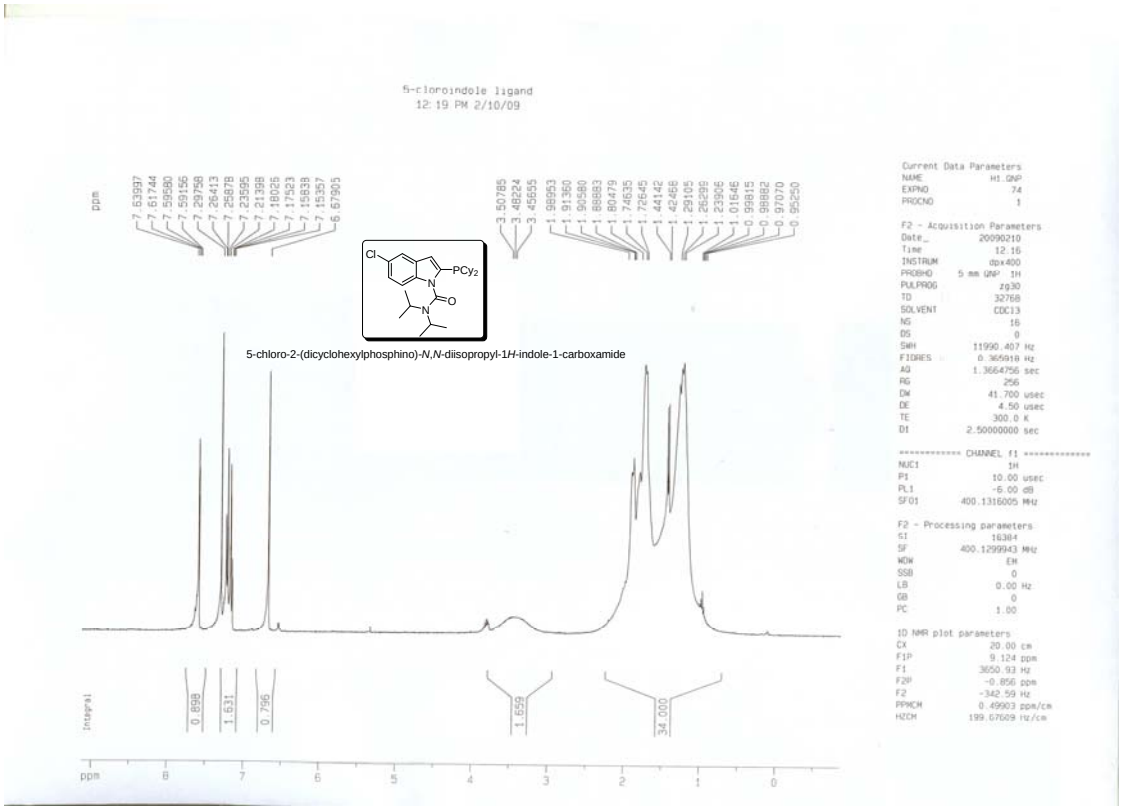
Mass spectrum of 5-chloro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



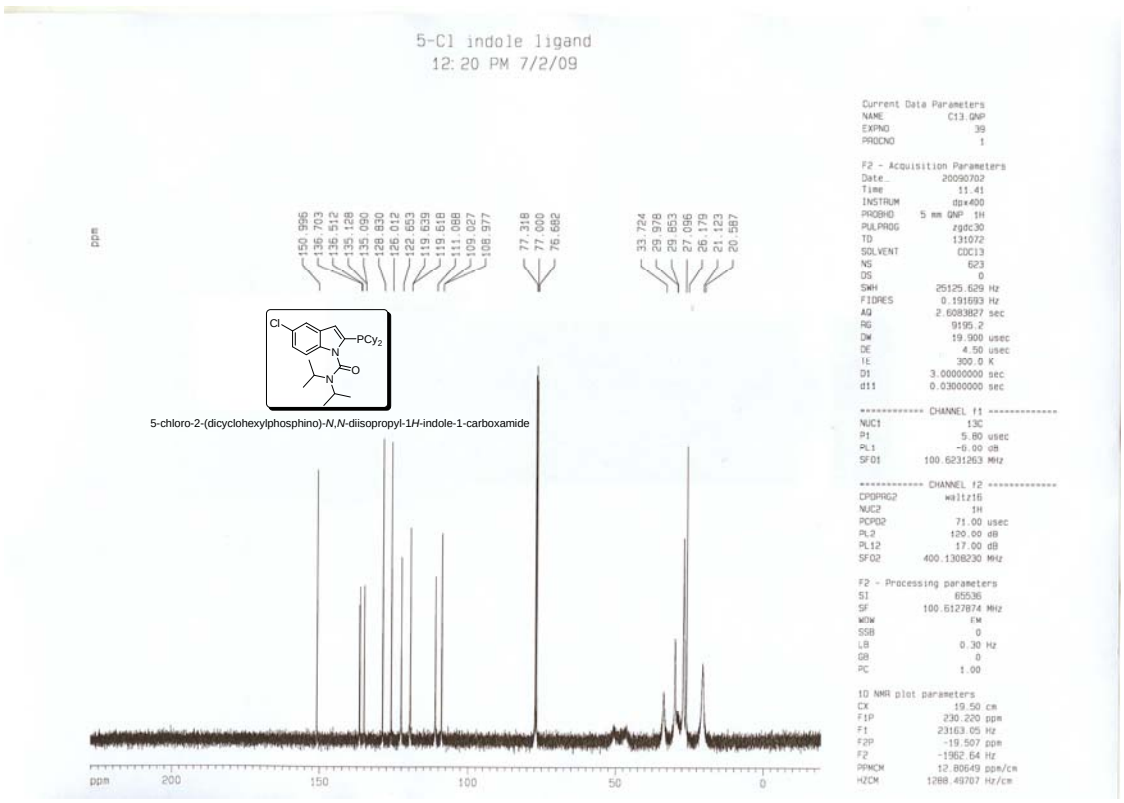
High resolution mass spectrum of 5-chloro-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



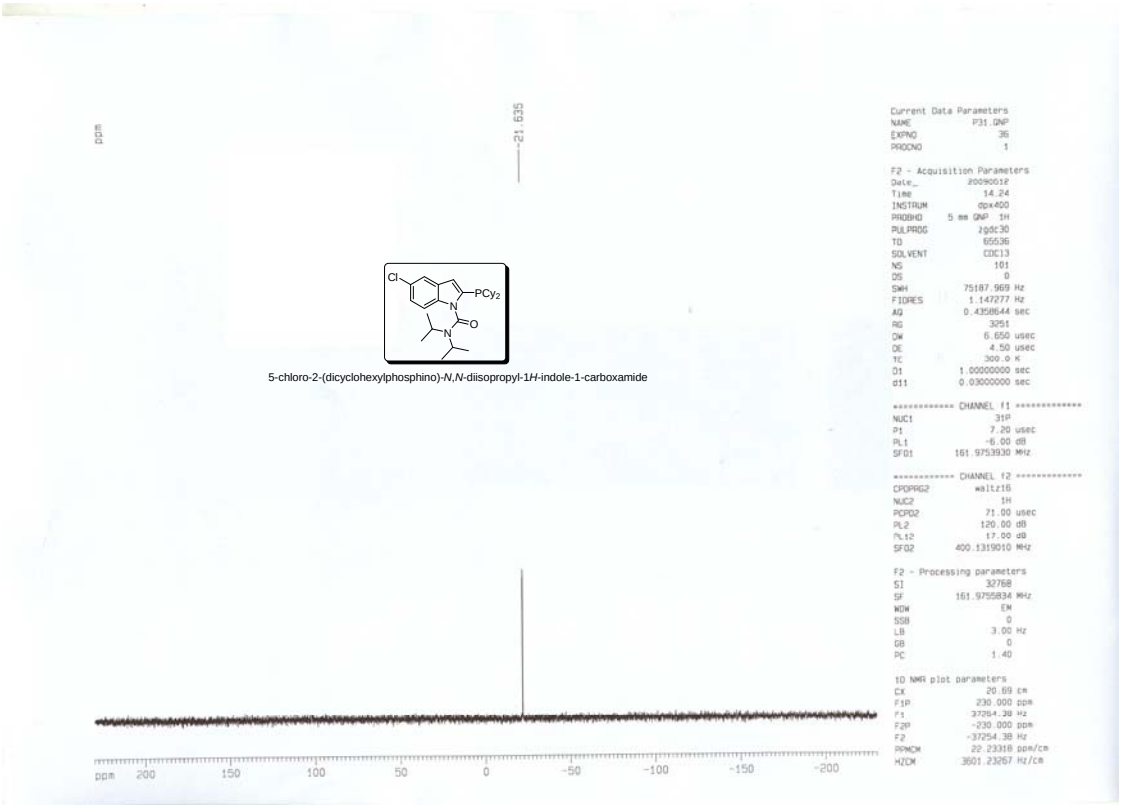
^{1}H NMR of 5-chloro-2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



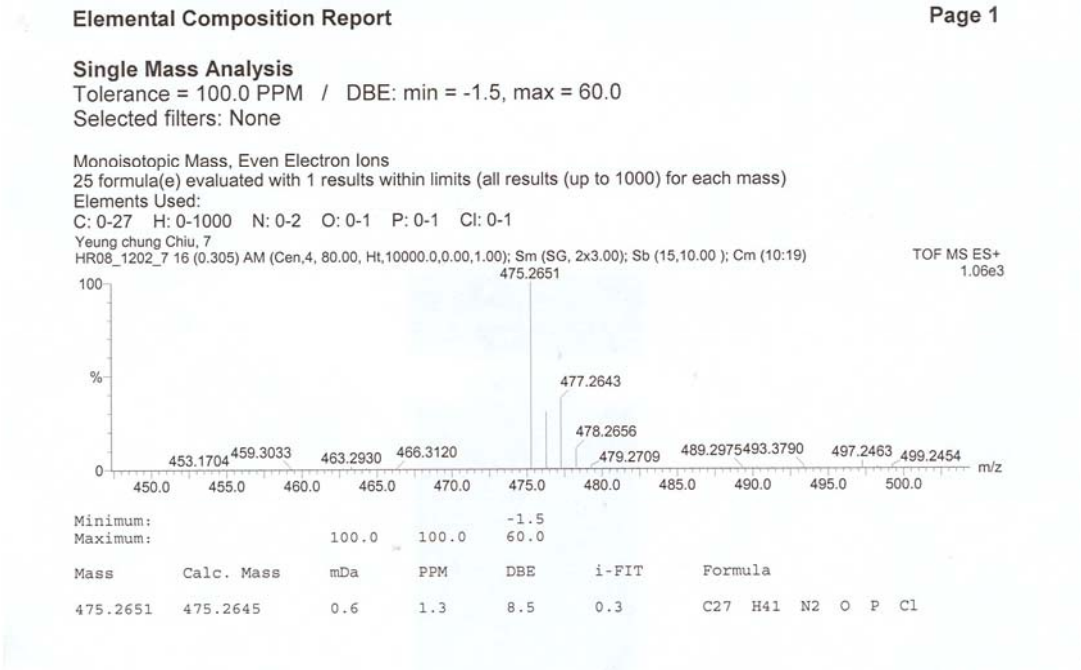
^{13}C NMR of 5-chloro-2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



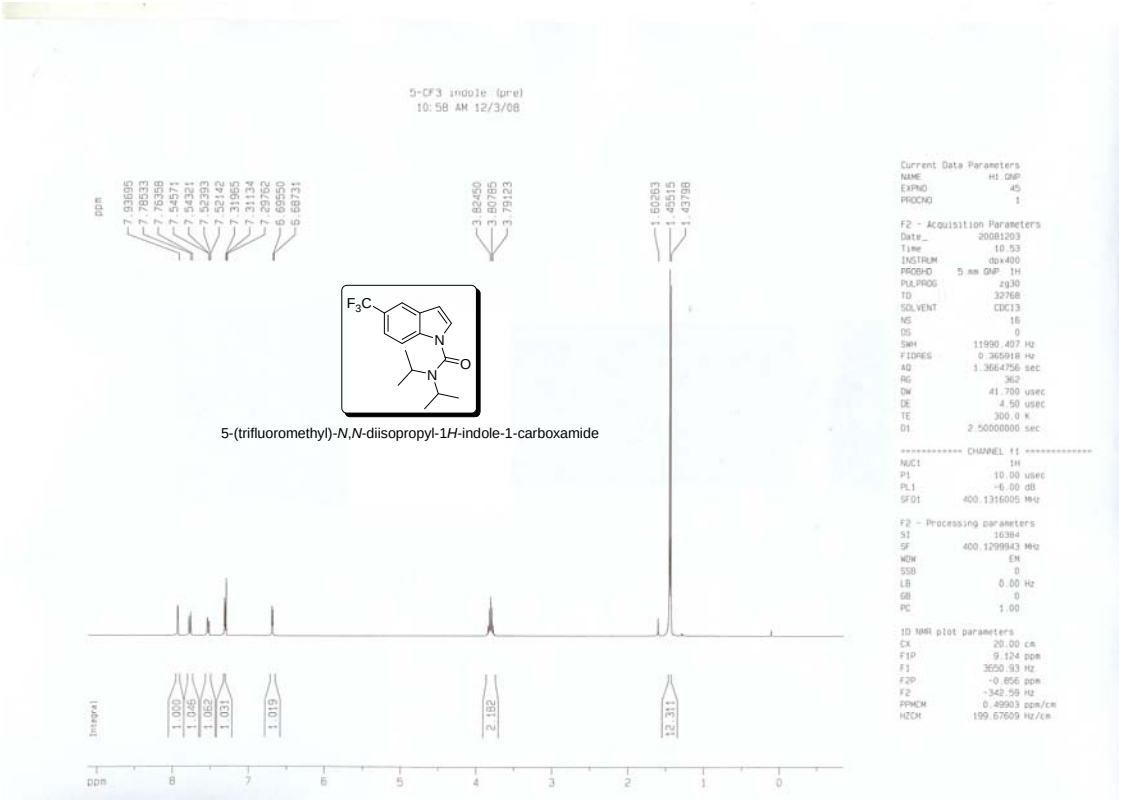
^{31}P NMR of 5-chloro-2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



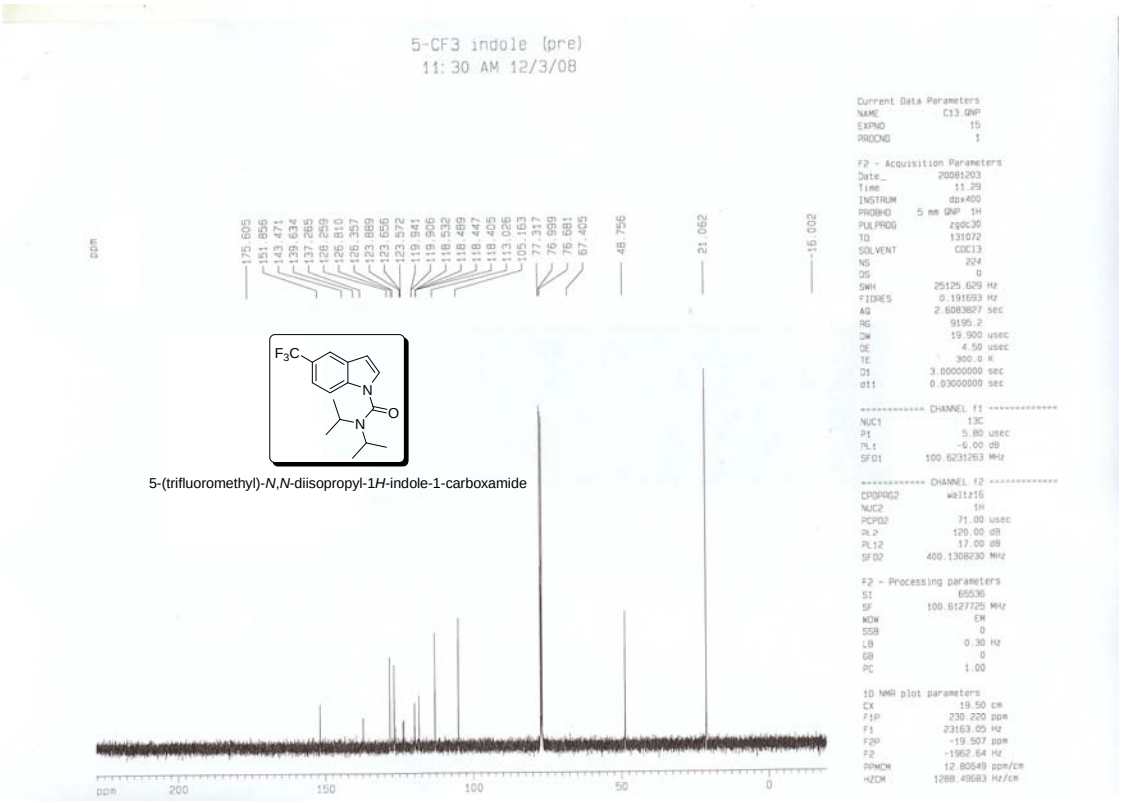
High resolution mass spectrum of 5-chloro-2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



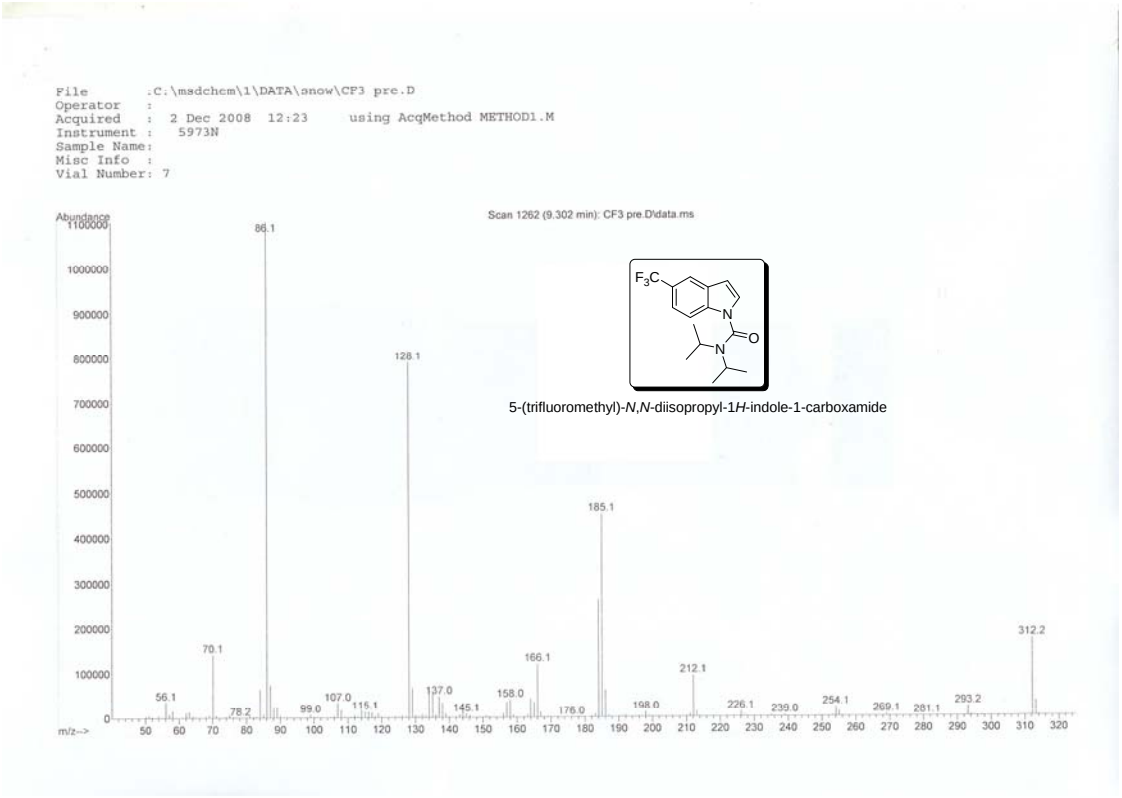
^{1}H NMR of 5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



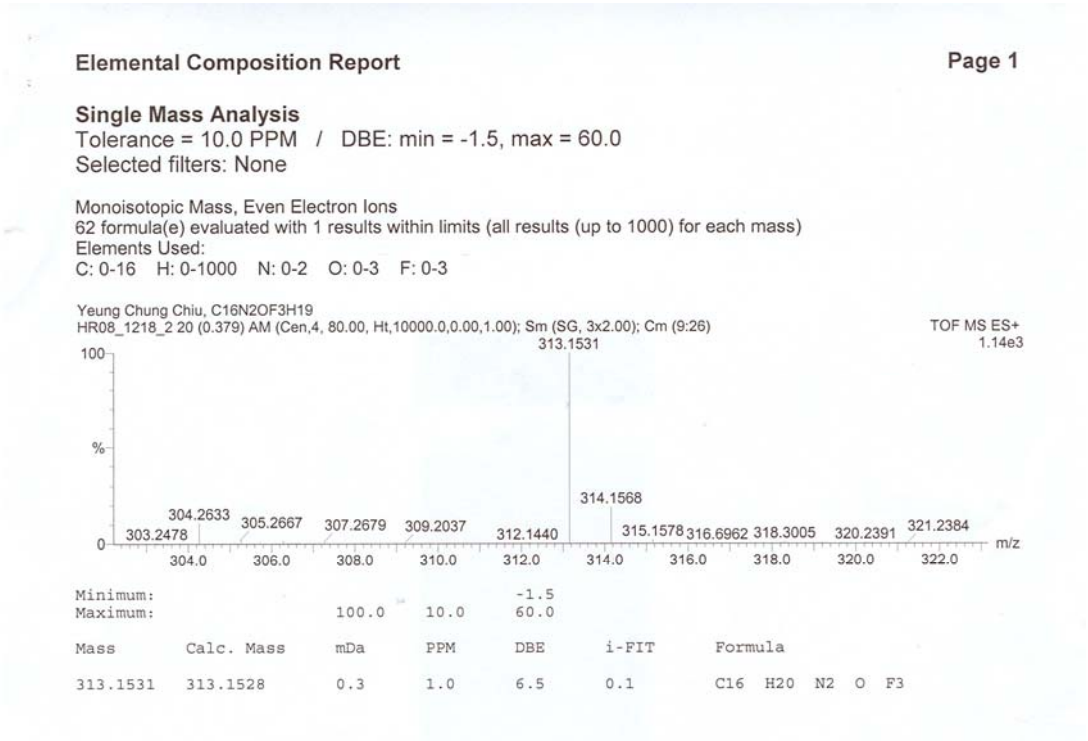
^{13}C NMR of 5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



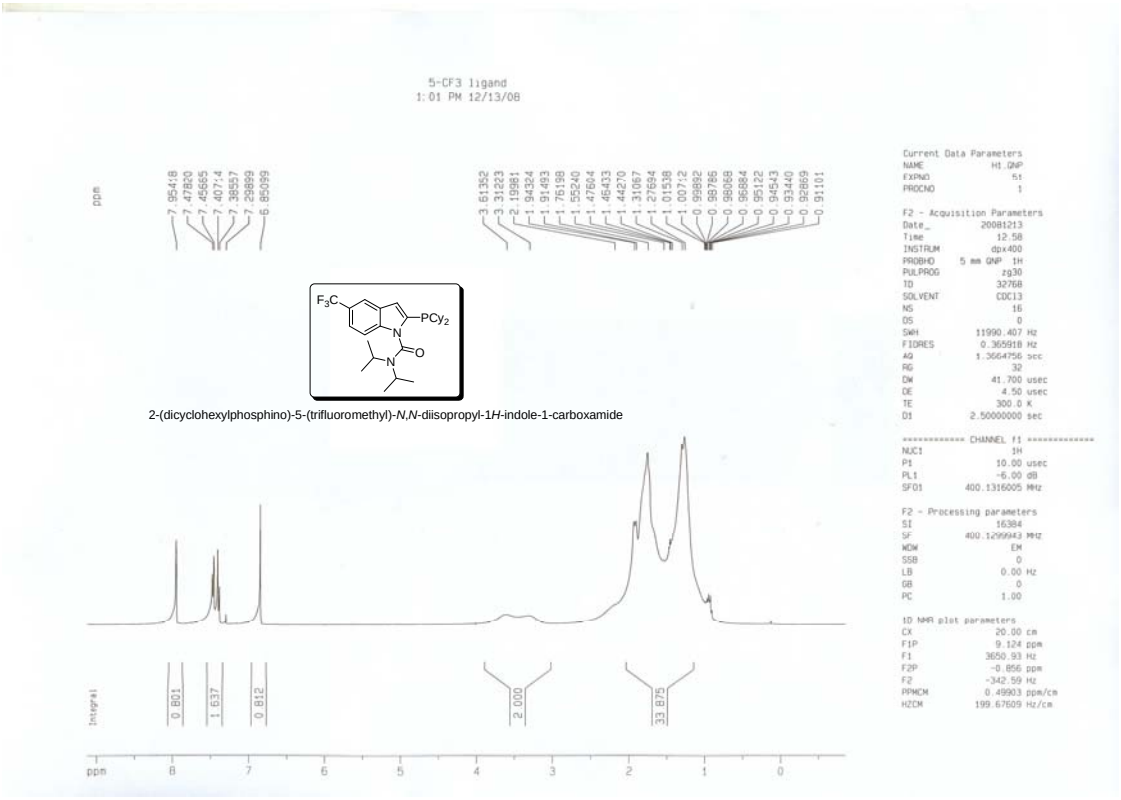
Mass spectrum of 5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



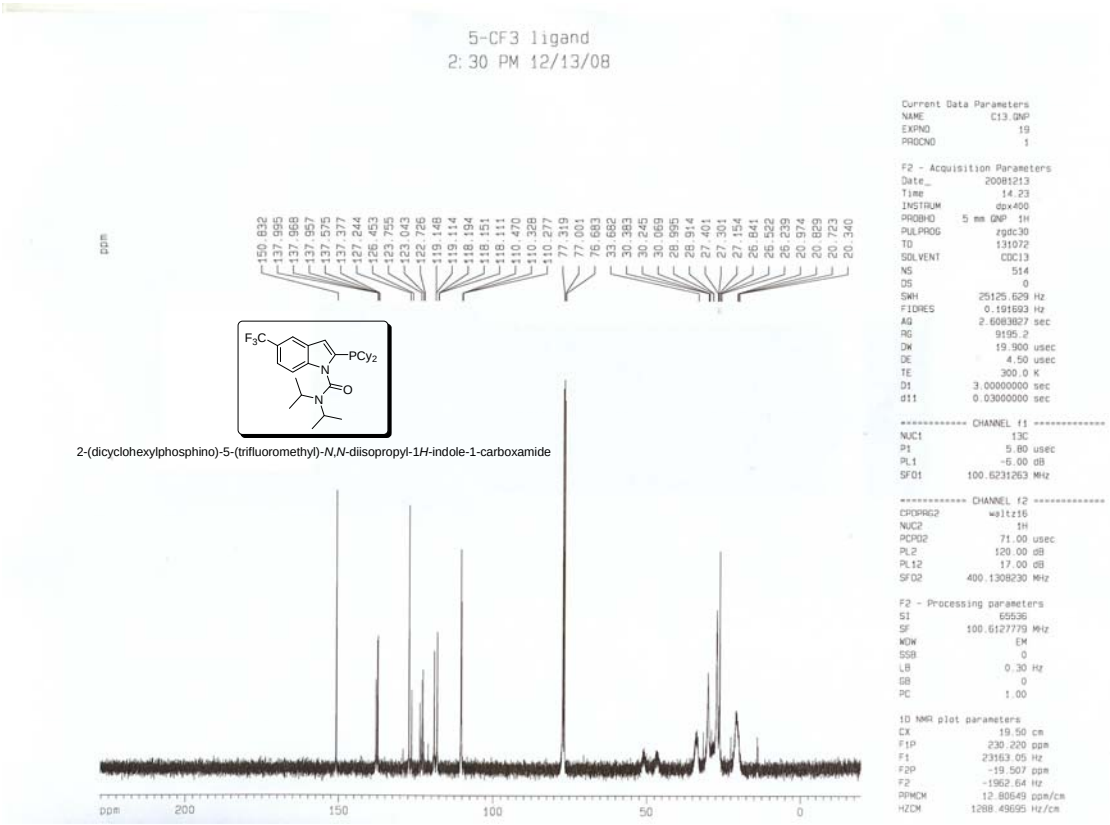
High resolution mass spectrum of 5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



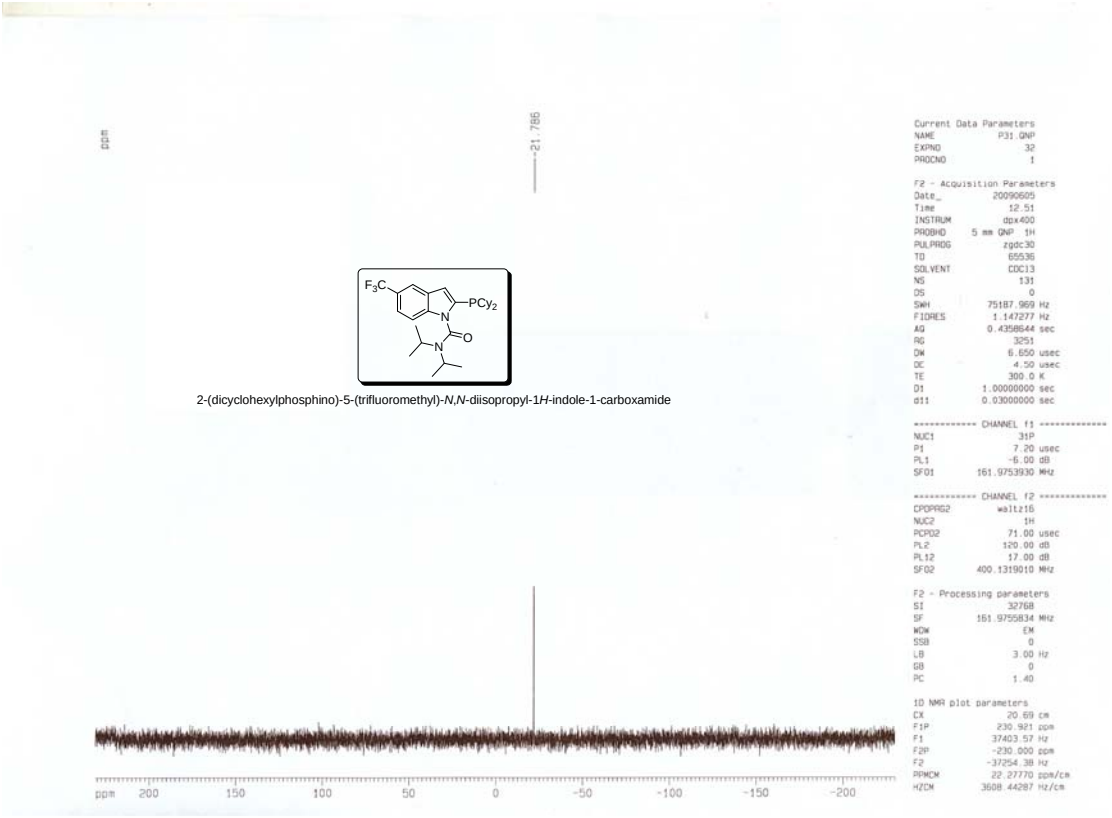
^{1}H NMR of 2-(dicyclohexylphosphino)-5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



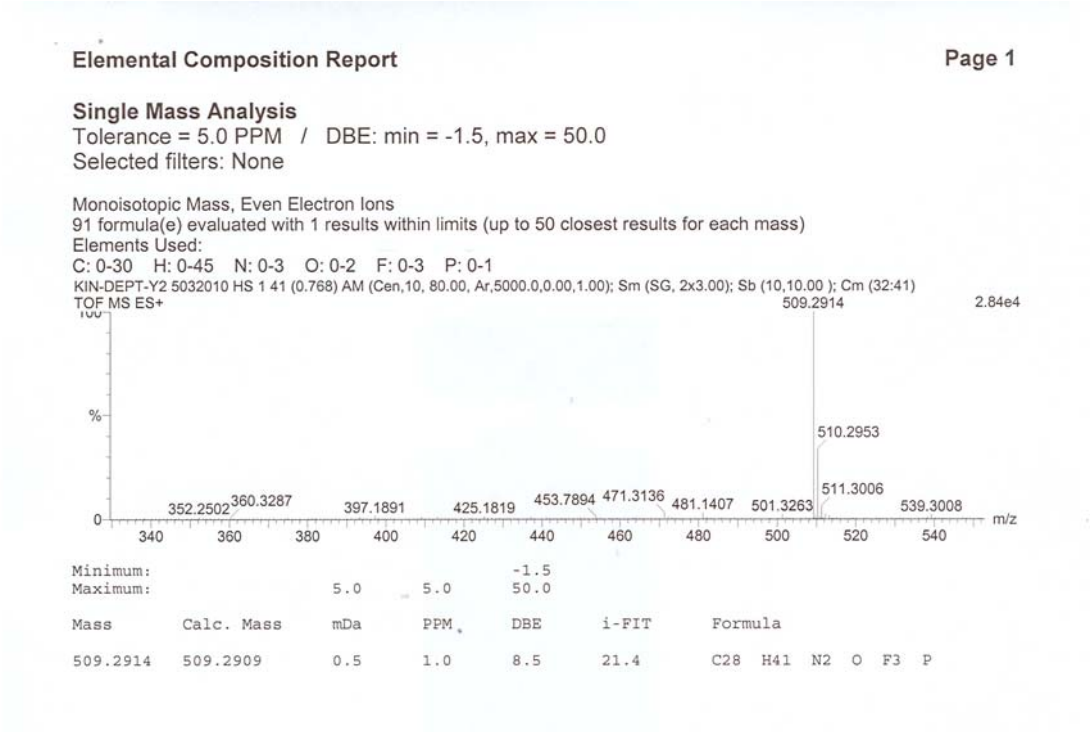
^{13}C NMR of 2-(dicyclohexylphosphino)-5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



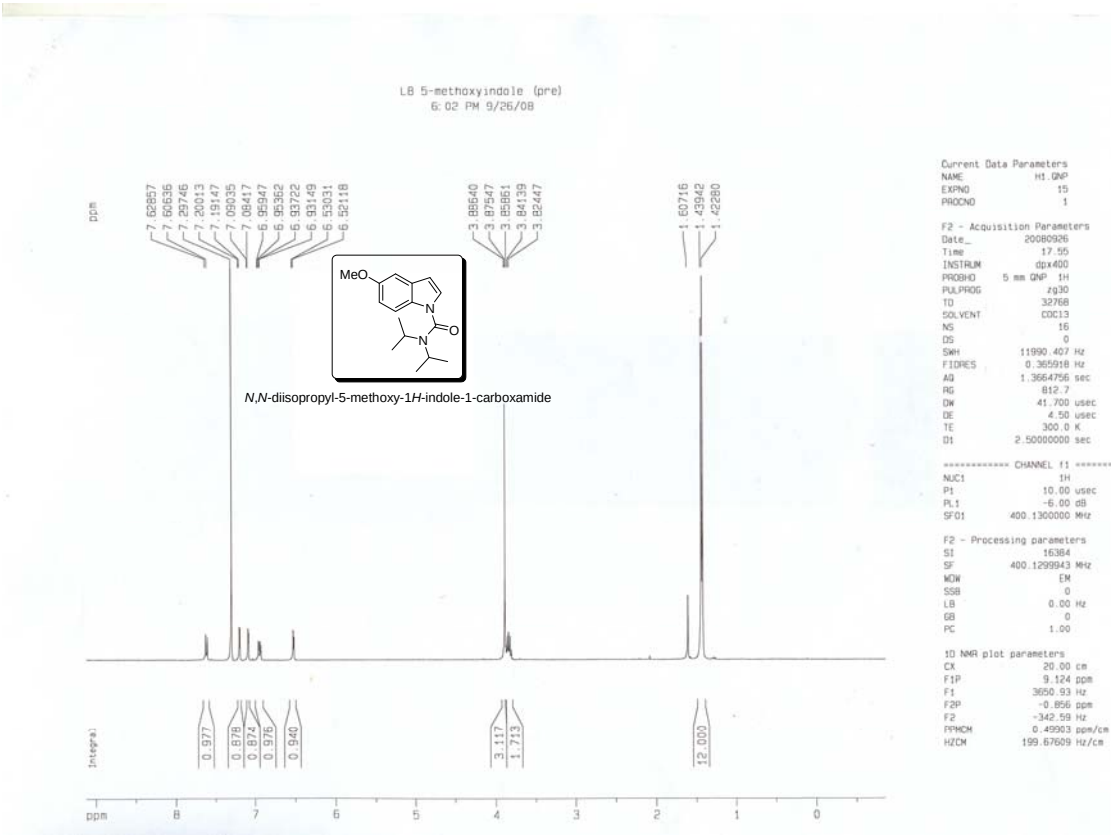
^{31}P NMR of 2-(dicyclohexylphosphino)-5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



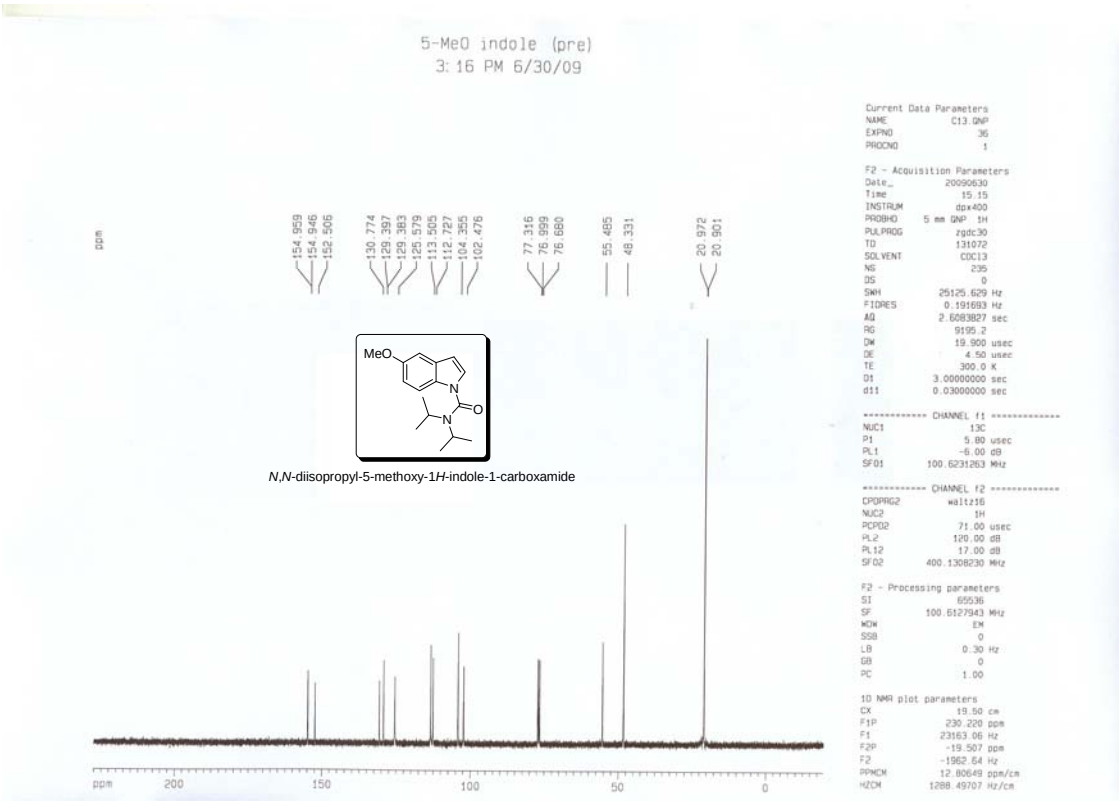
High resolution mass spectrum of 2-(dicyclohexylphosphino)-5-(trifluoromethyl)-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



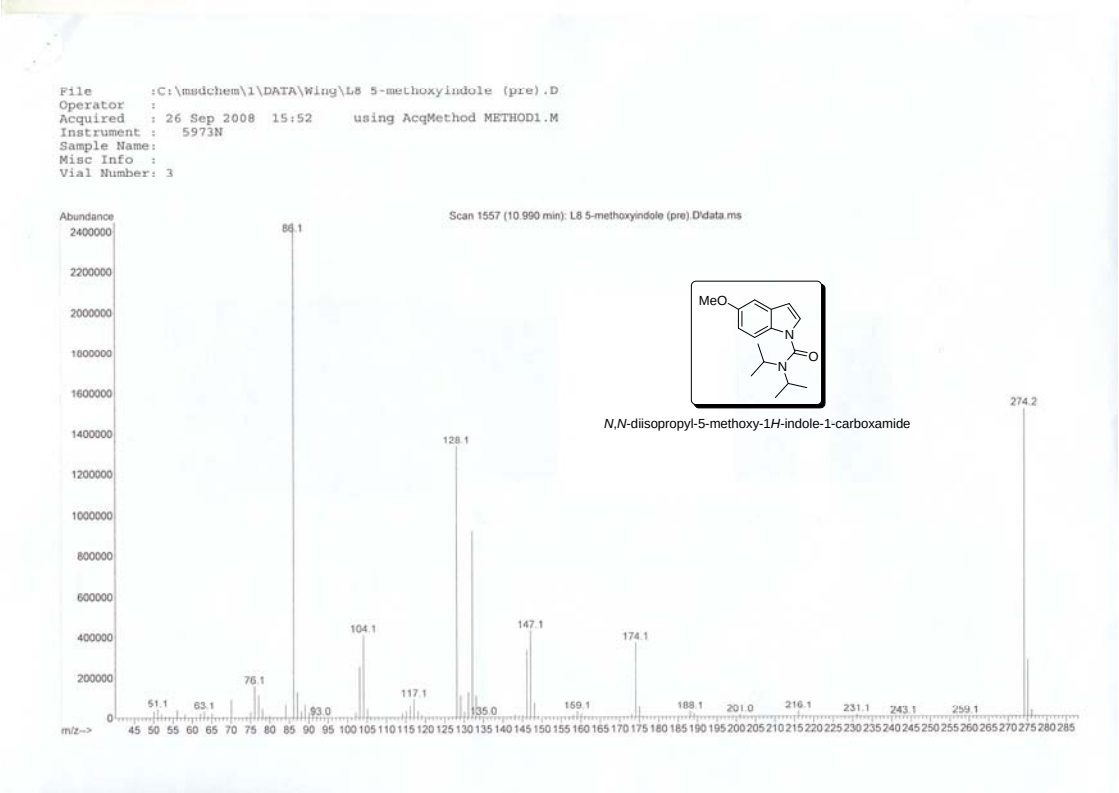
^{1}H NMR of *N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



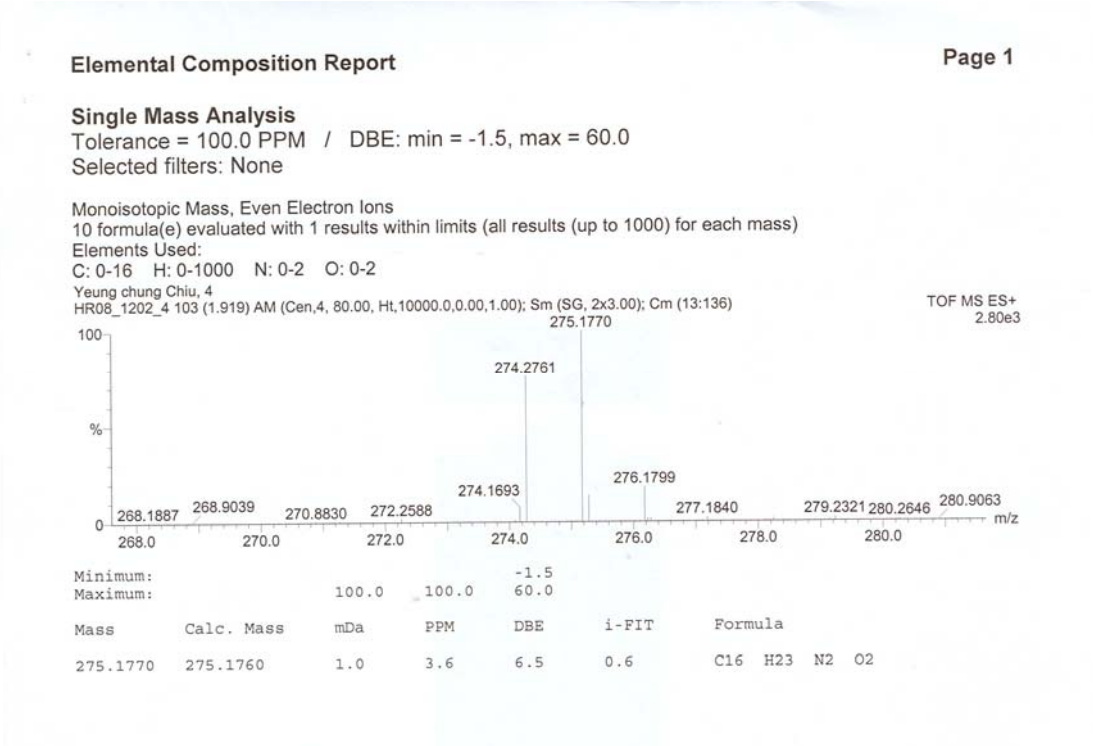
^{13}C NMR of *N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



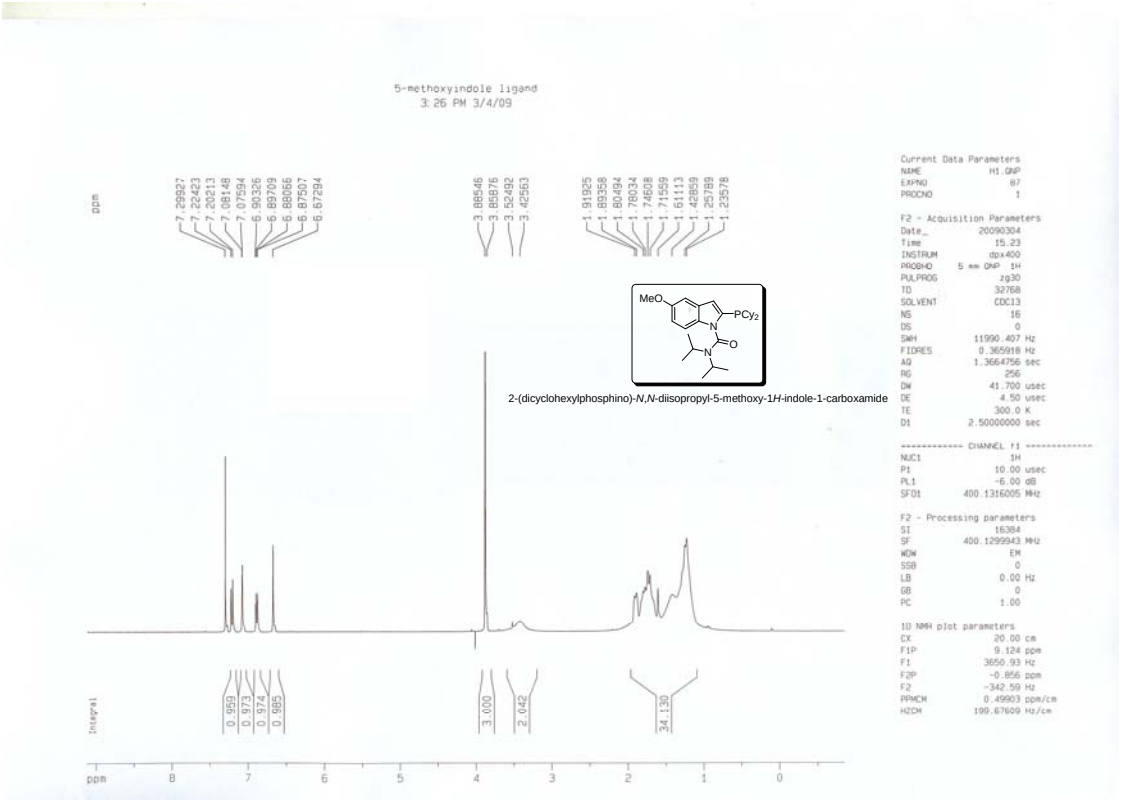
Mass spectrum of *N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



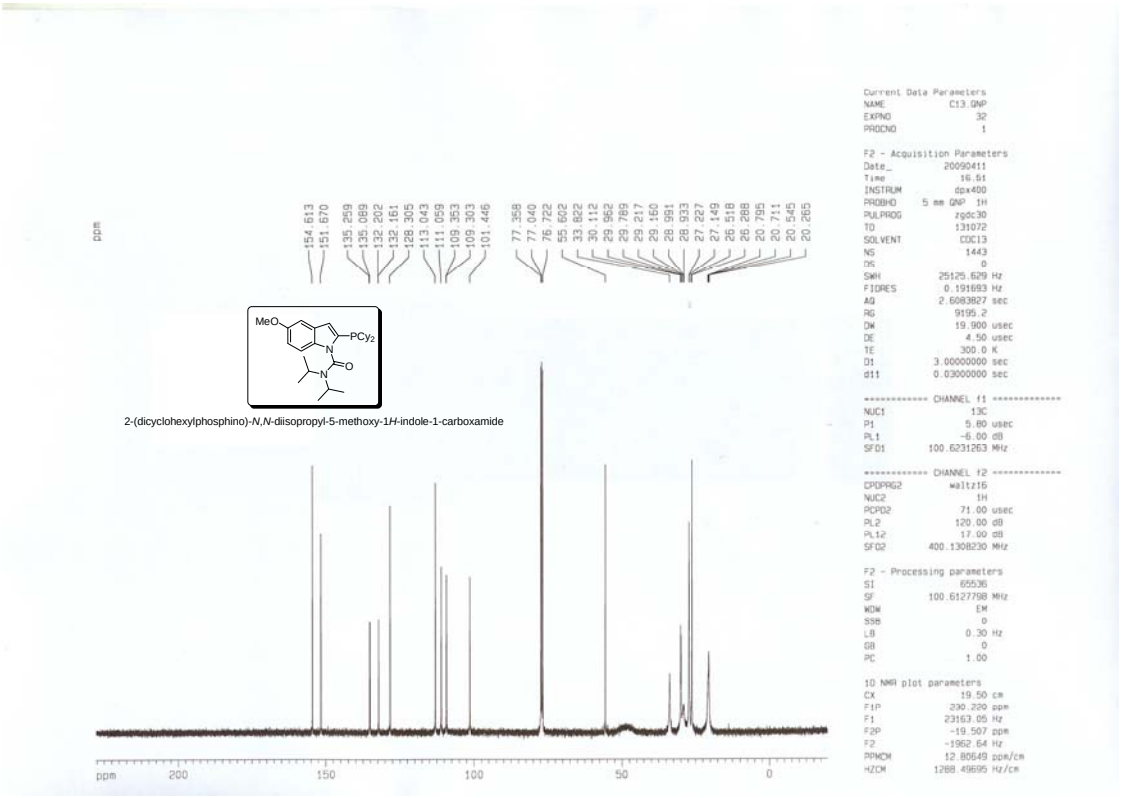
High resolution mass spectrum of *N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



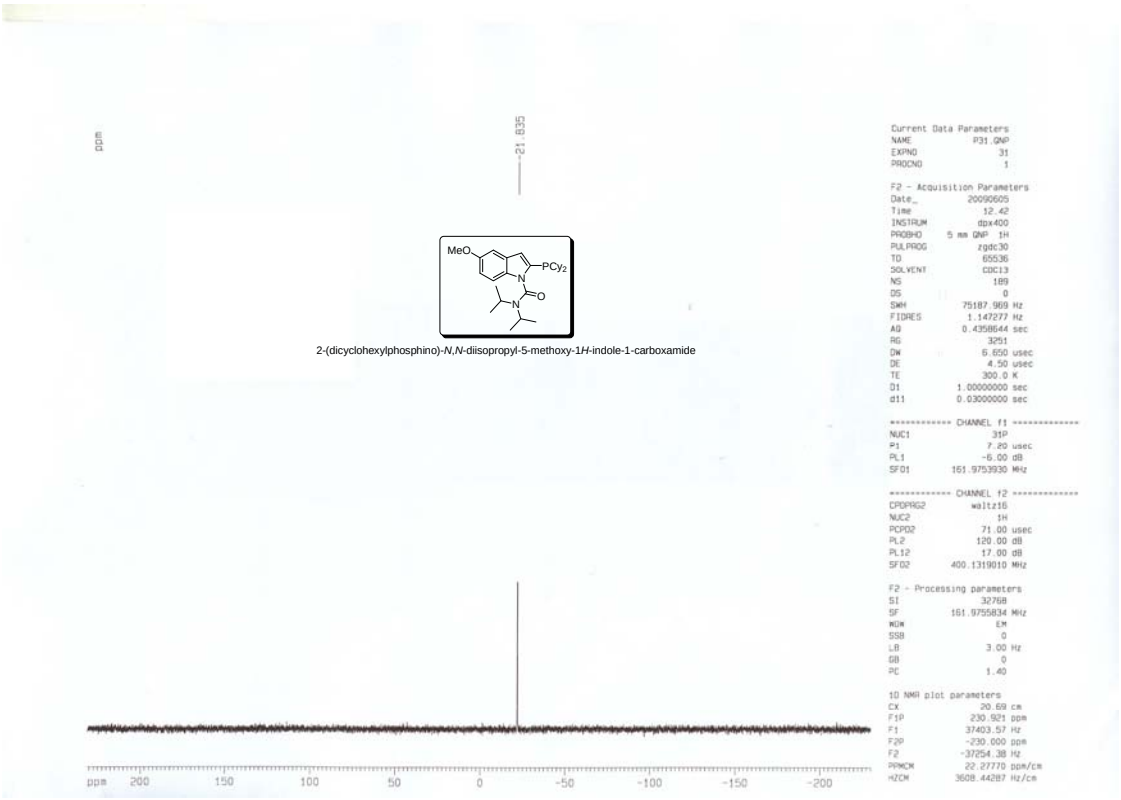
^{1}H NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



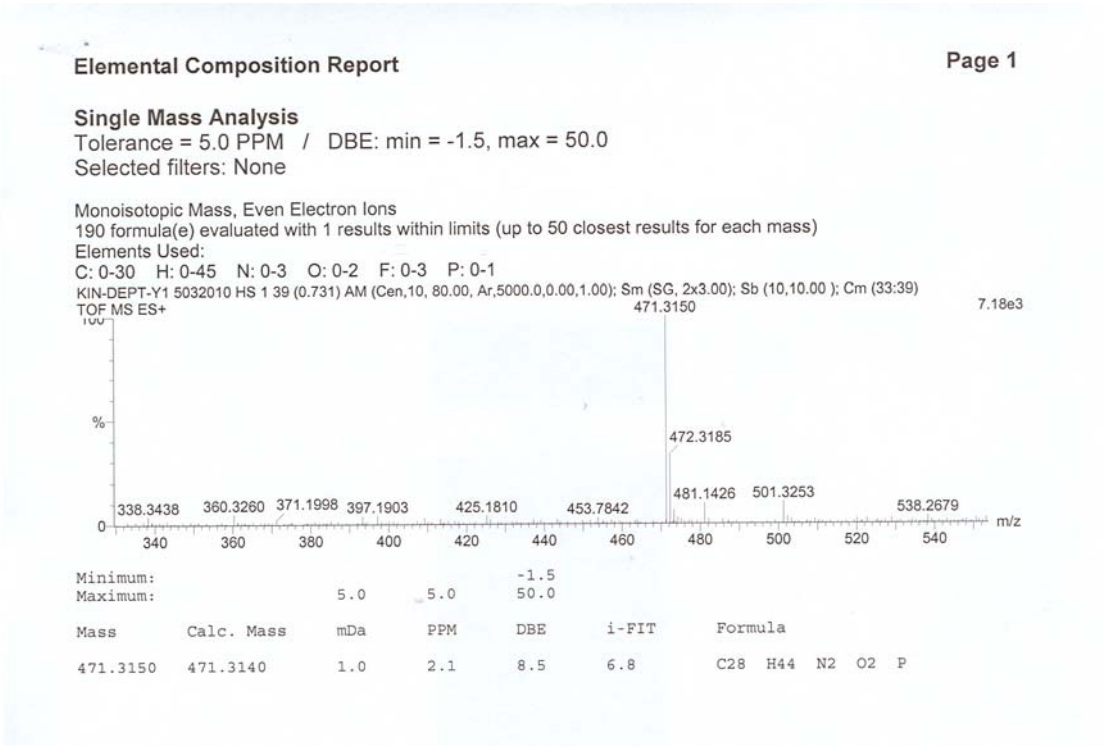
^{13}C NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



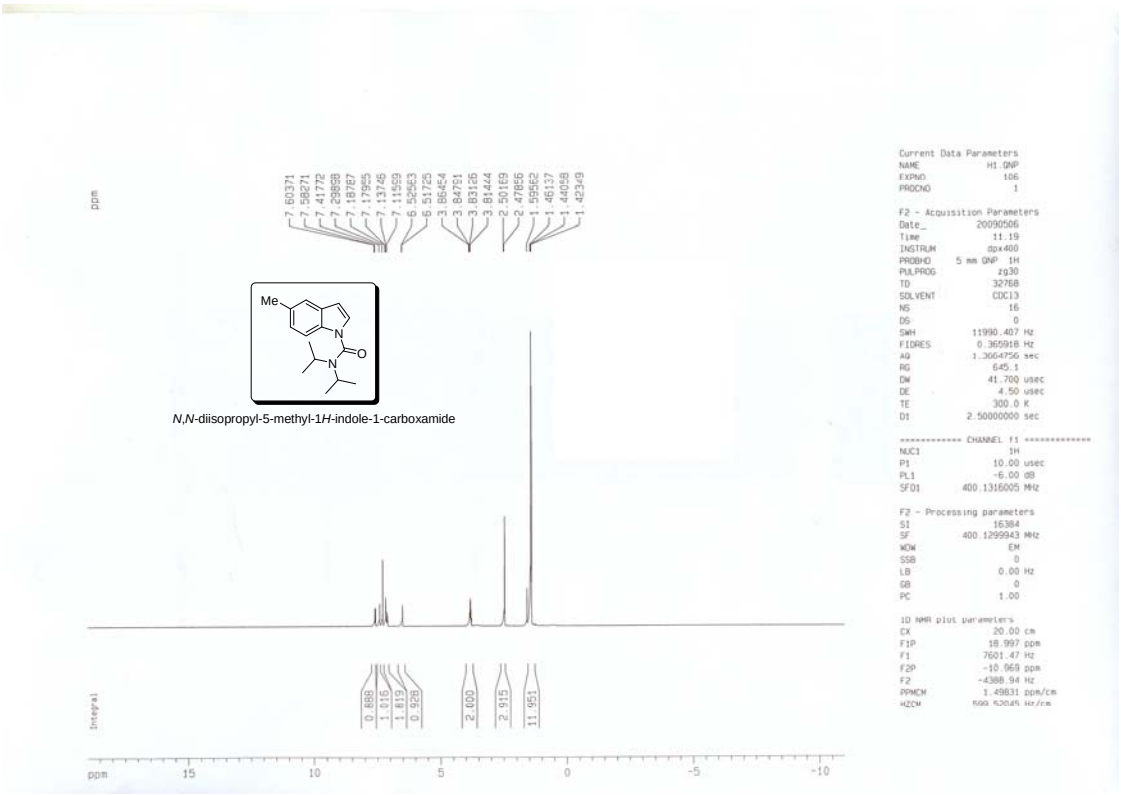
^{31}P NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



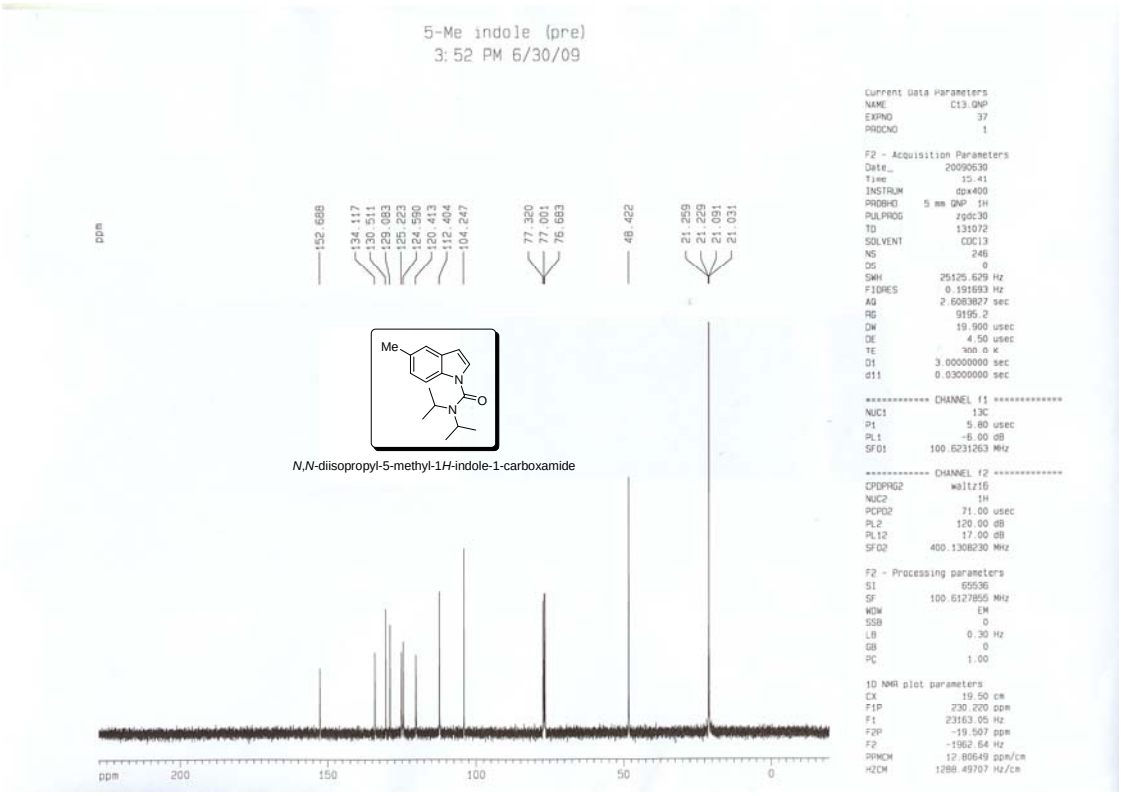
High resolution mass spectrum of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



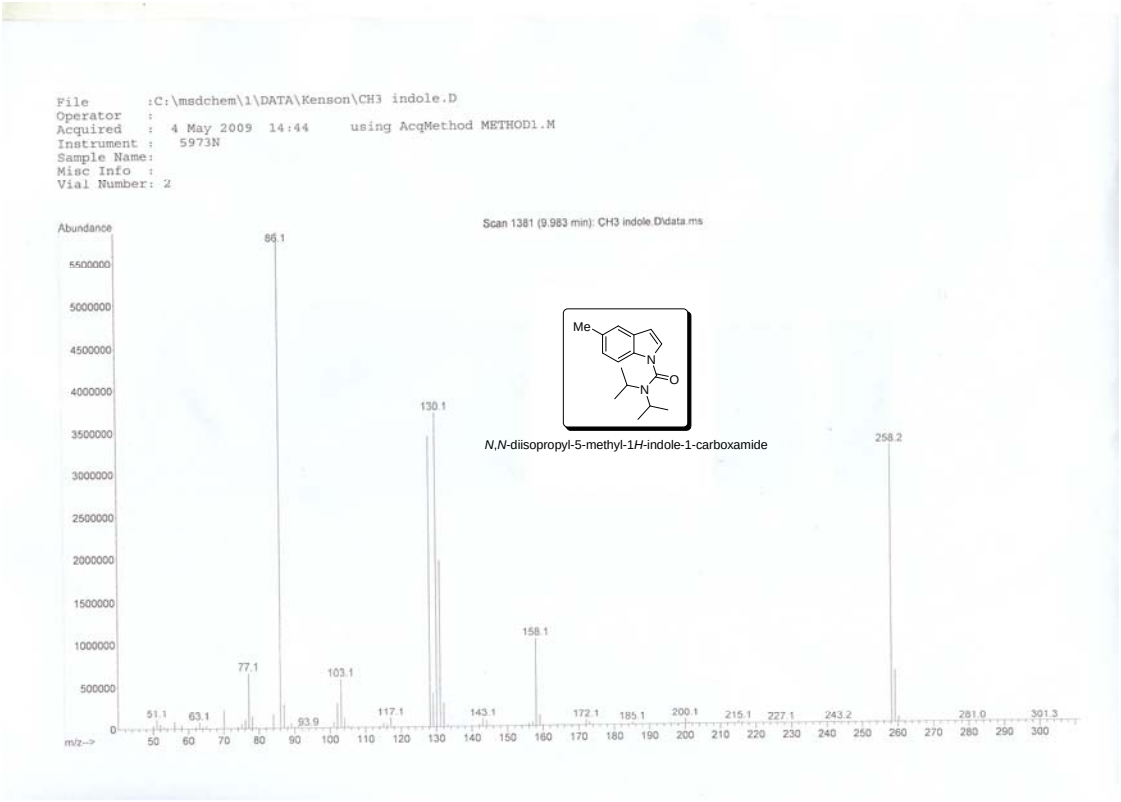
^{1}H NMR of *N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide



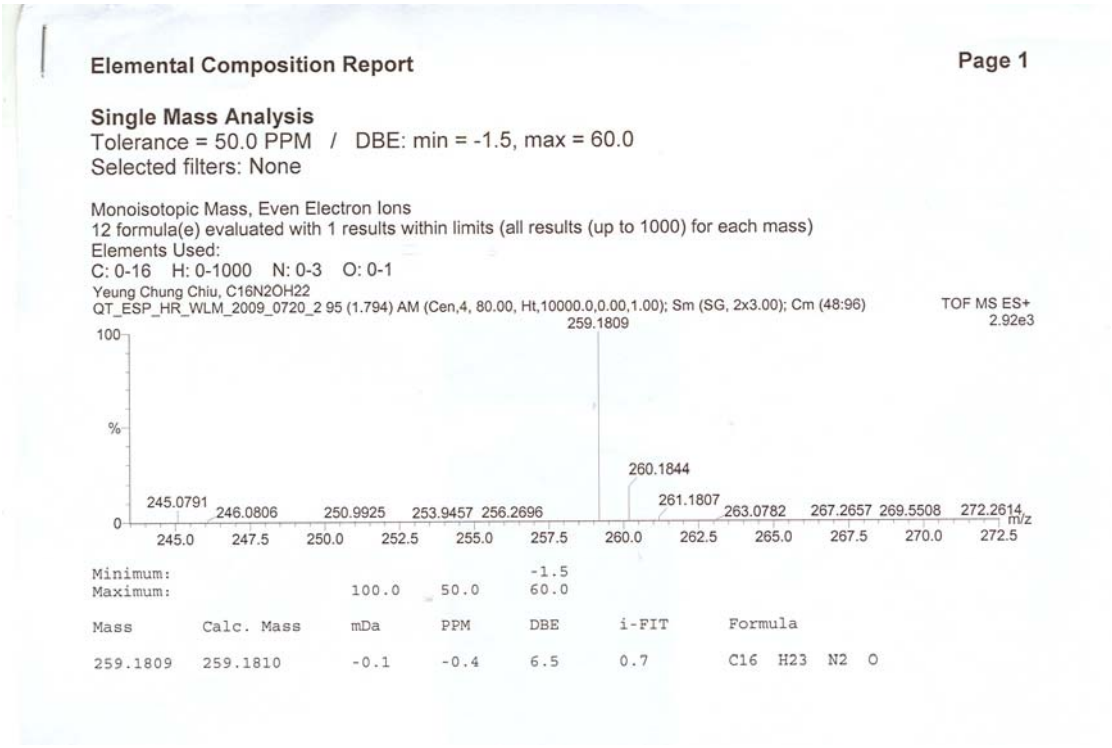
^{13}C NMR of *N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide



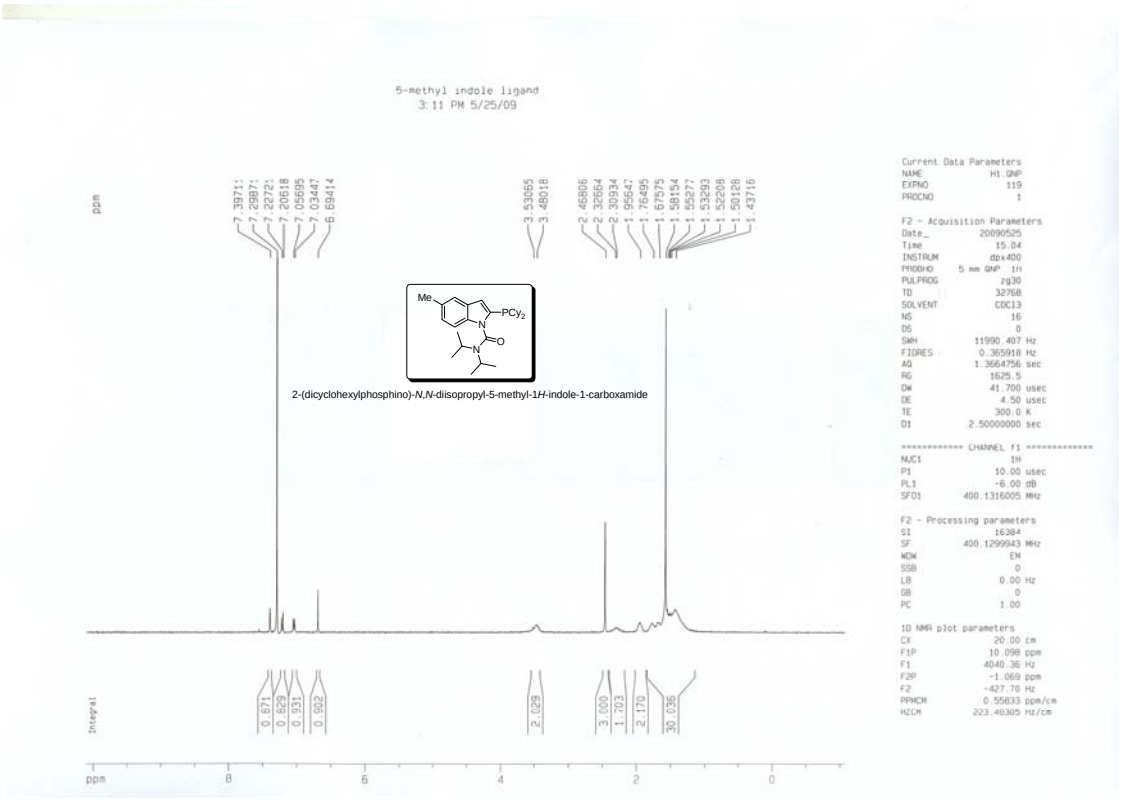
Mass spectrum of *N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide



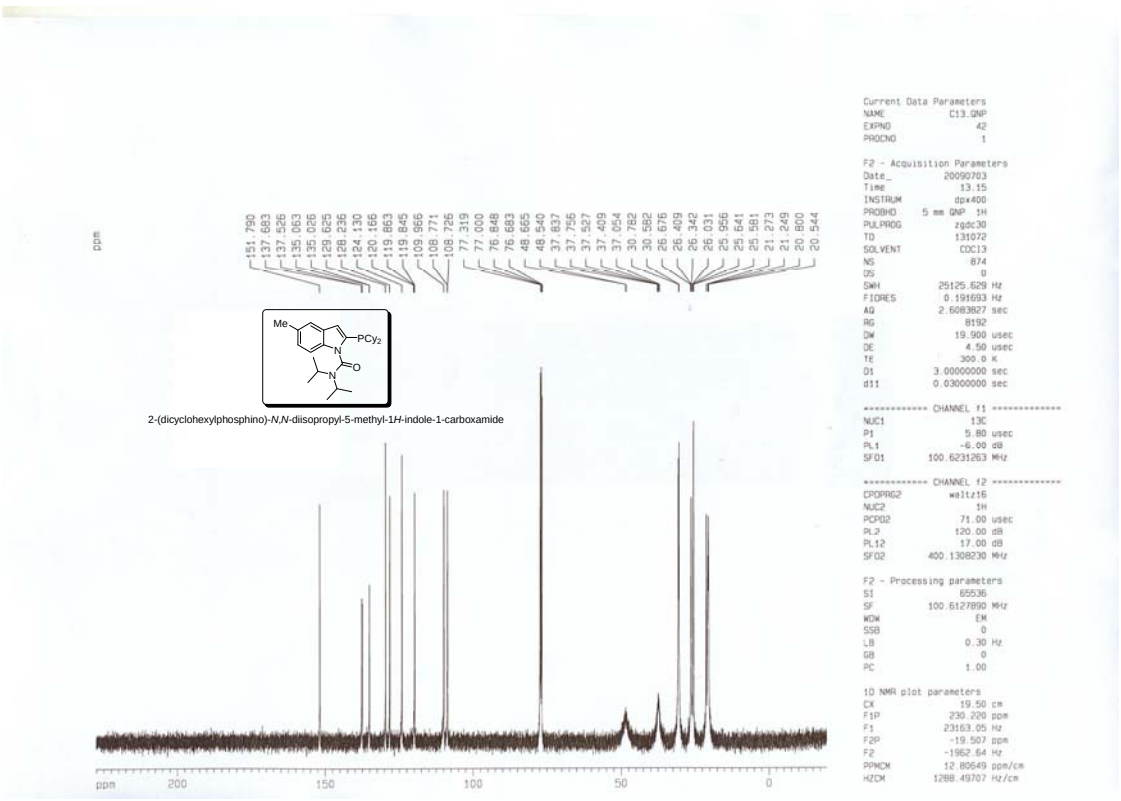
High resolution mass spectrum of *N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide



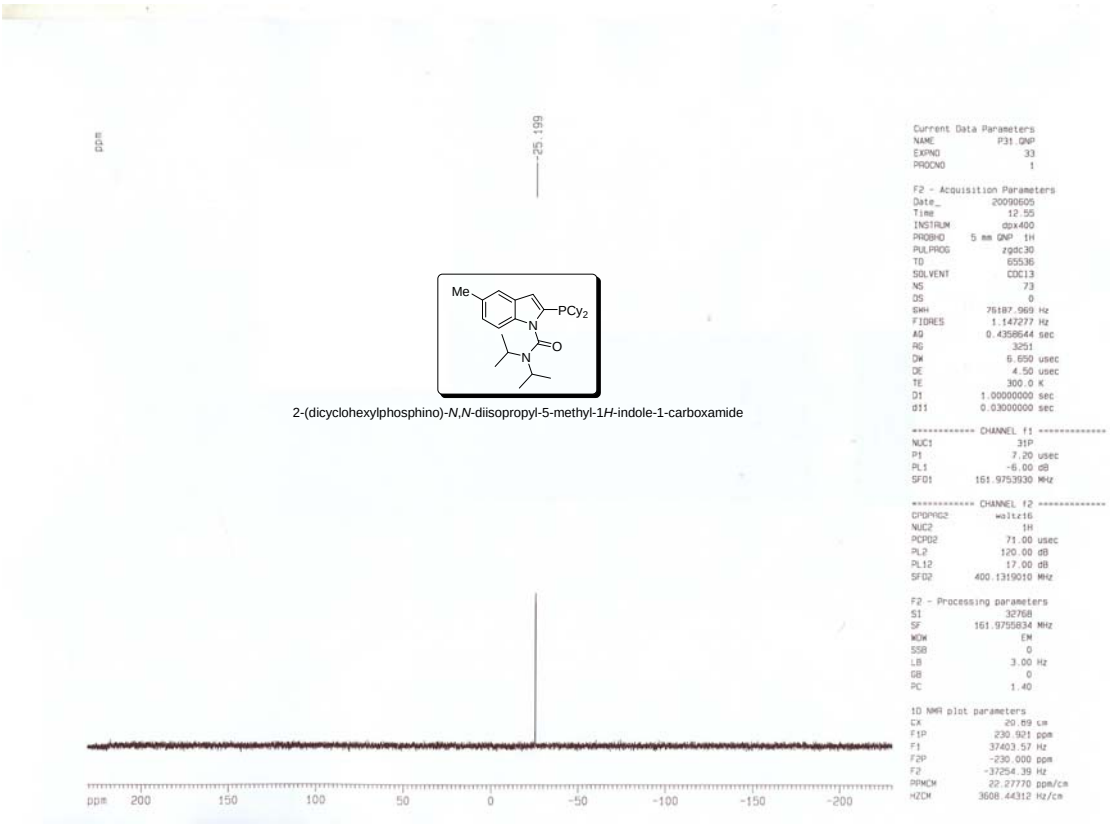
^{1}H NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide



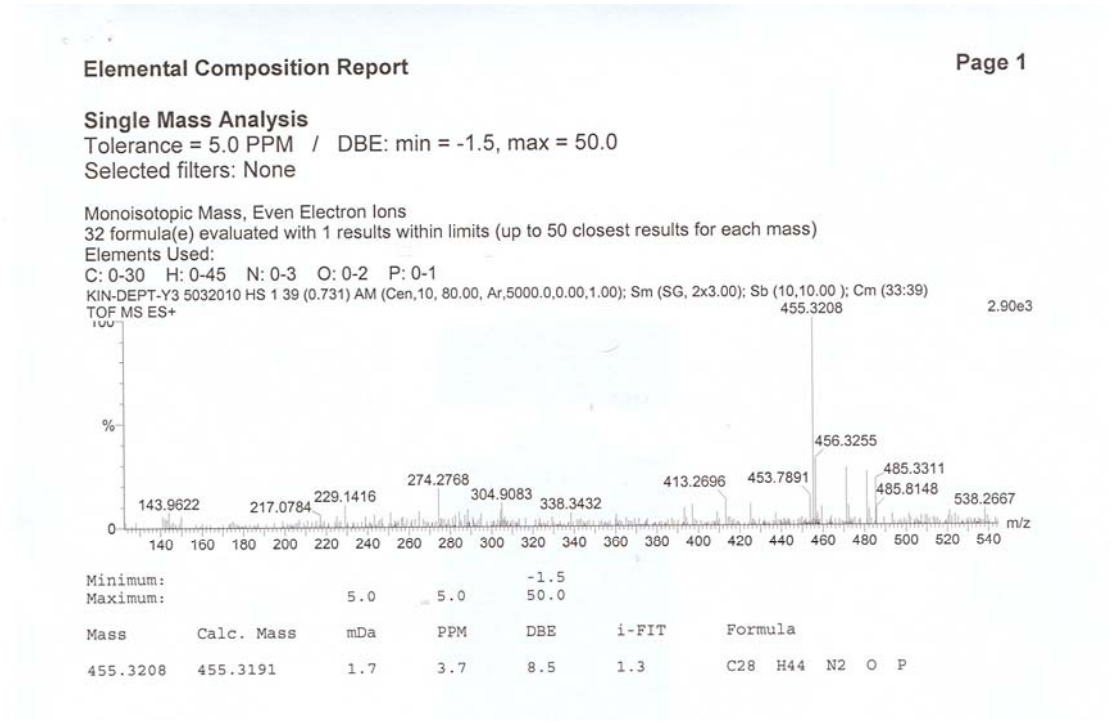
^{13}C NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide



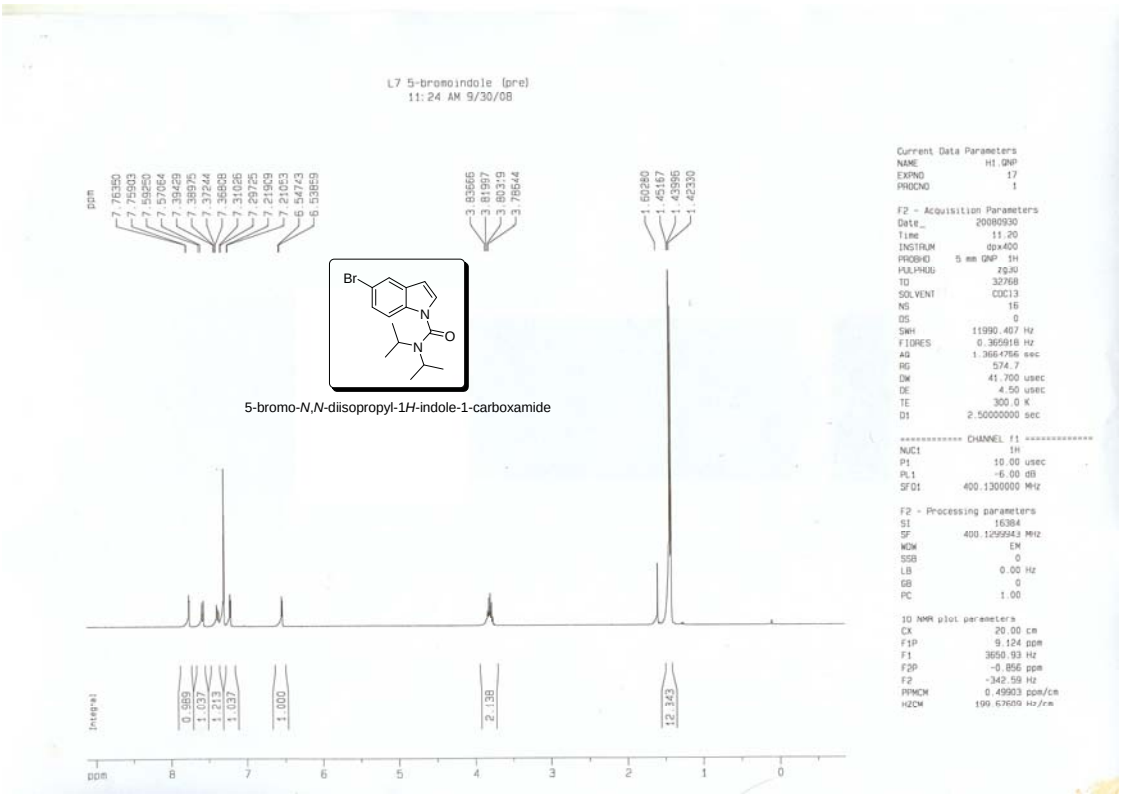
^{31}P NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide



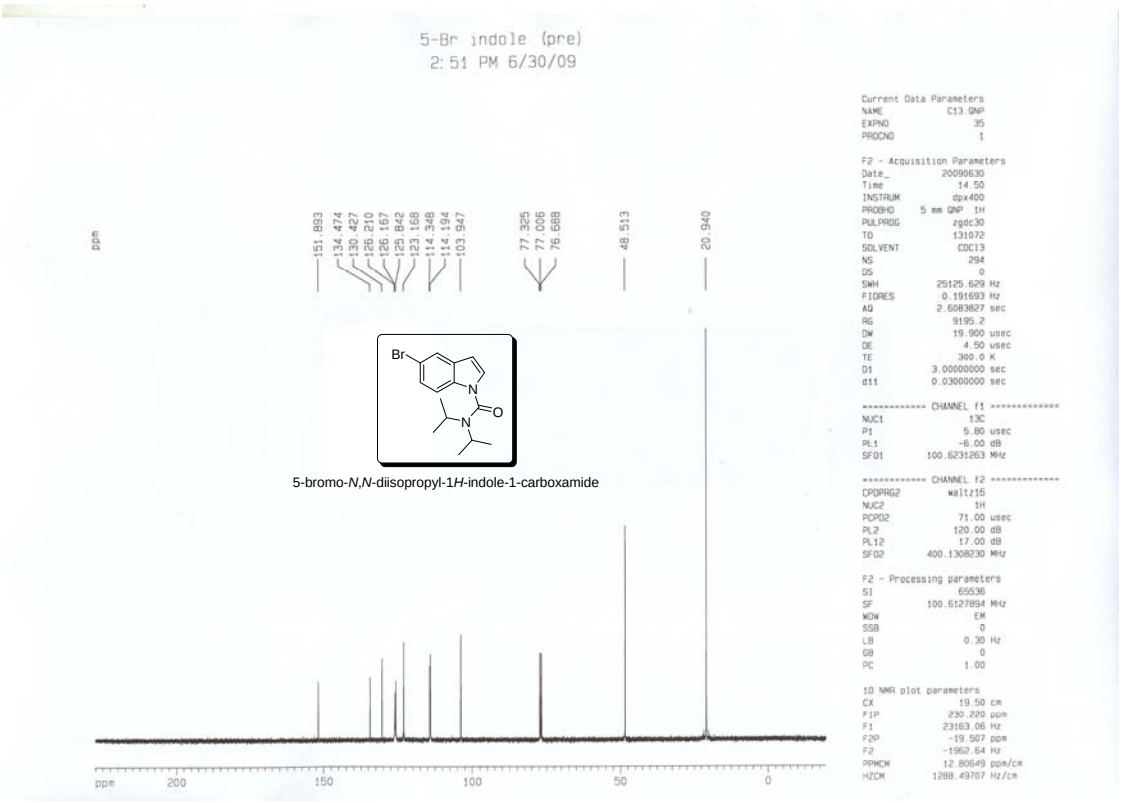
High resolution mass spectrum of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-methyl-1H-indole-1-carboxamide



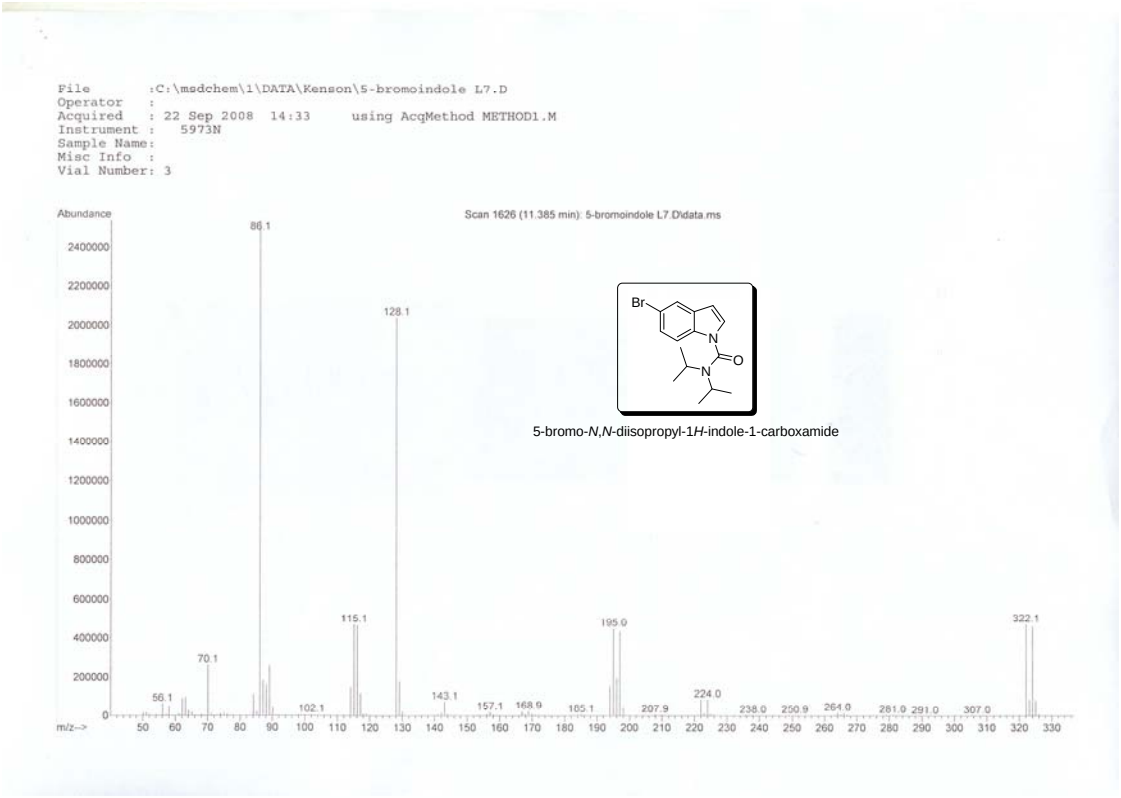
^{1}H NMR of 5-bromo-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



^{13}C NMR of 5-bromo-*N*,*N*-diisopropyl-1H-indole-1-carboxamide

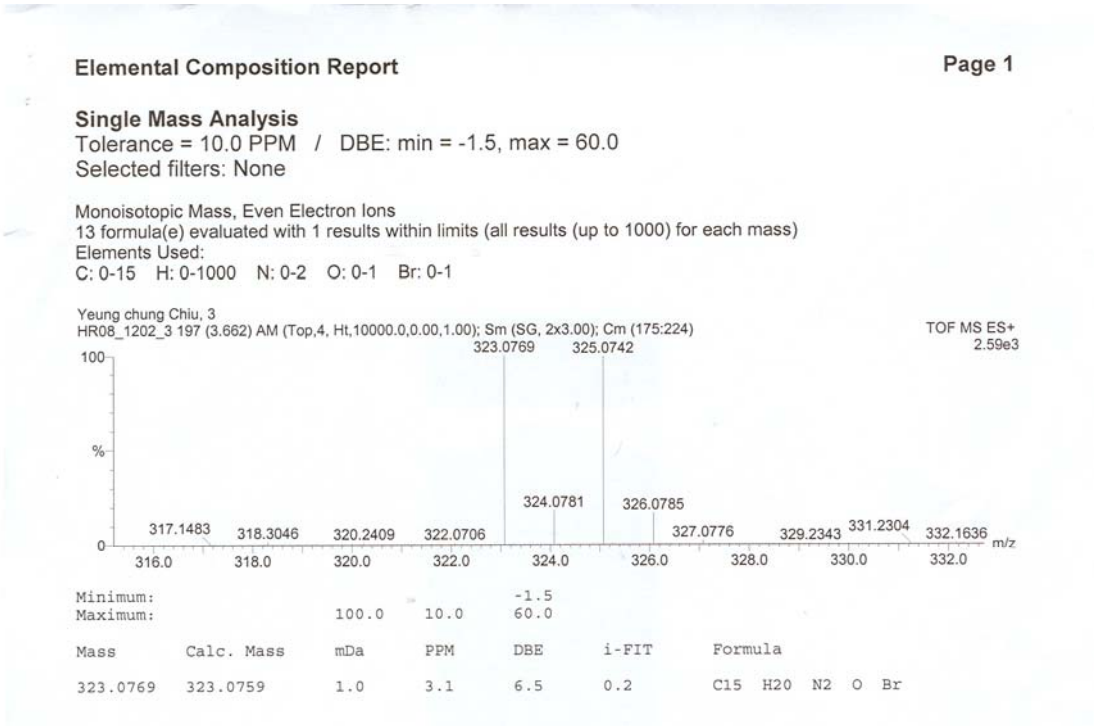


Mass spectrum of 5-bromo-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



5-bromo-*N*,*N*-diisopropyl-1*H*-indole-1-carboxamide

High resolution mass spectrum of 5-bromo-*N*,*N*-diisopropyl-1H-indole-1-carboxamide



Elemental Composition Report Page 1

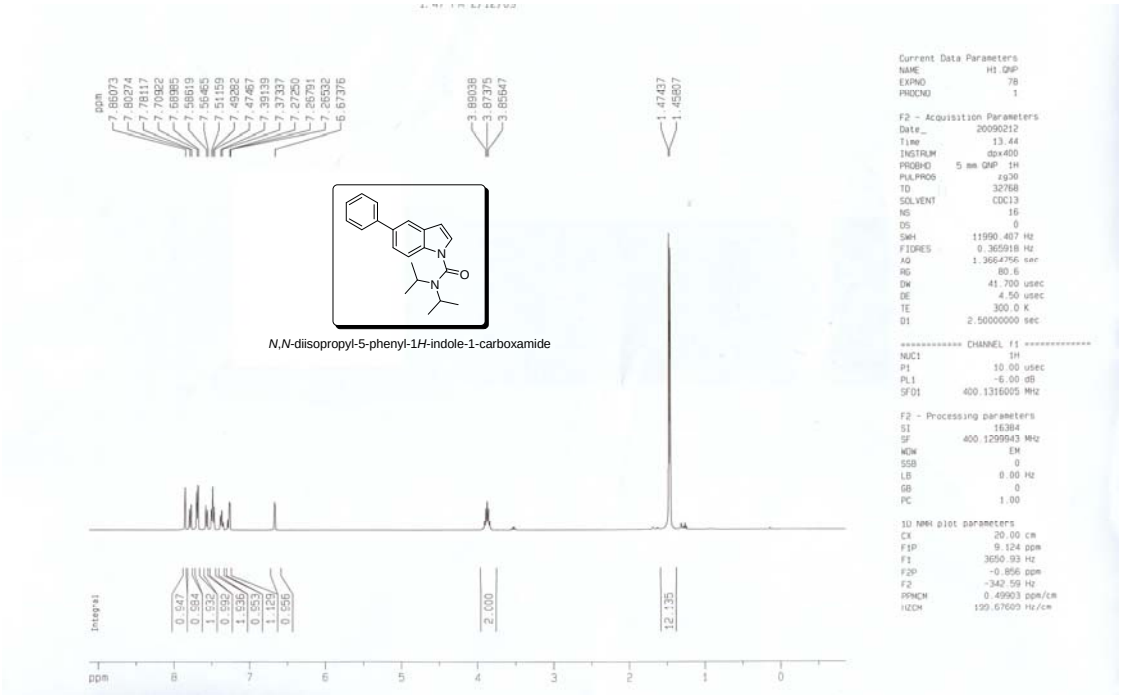
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-15 H: 0-1000 N: 0-2 O: 0-1 Br: 0-1

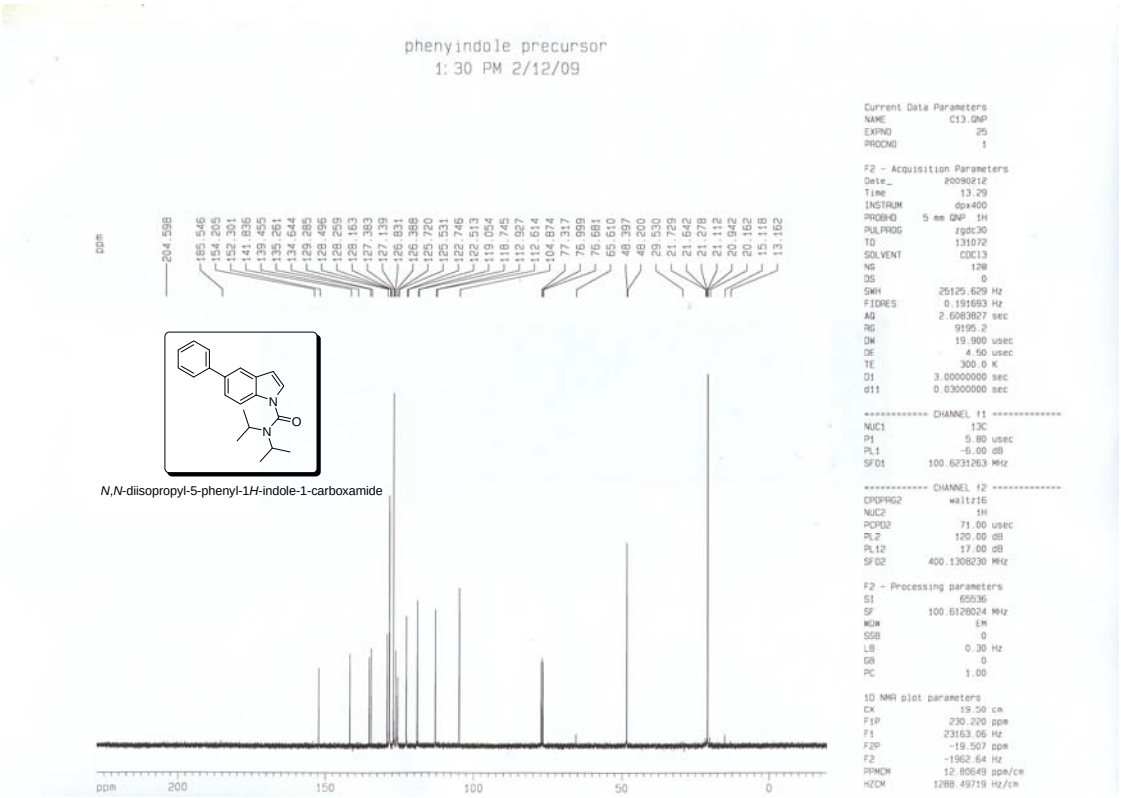
Yeung chung Chiu, 3
HR08_1202_3 197 (3.662) AM (Top,4, Ht,10000.0,0.00,1.00); Sm (SG, 2x3.00); Cm (175:224)
TOF MS ES+
2.59e3

Minimum:				-1.5		
Maximum:		100.0	10.0	60.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
323.0769	323.0759	1.0	3.1	6.5	0.2	C15 H20 N2 O Br

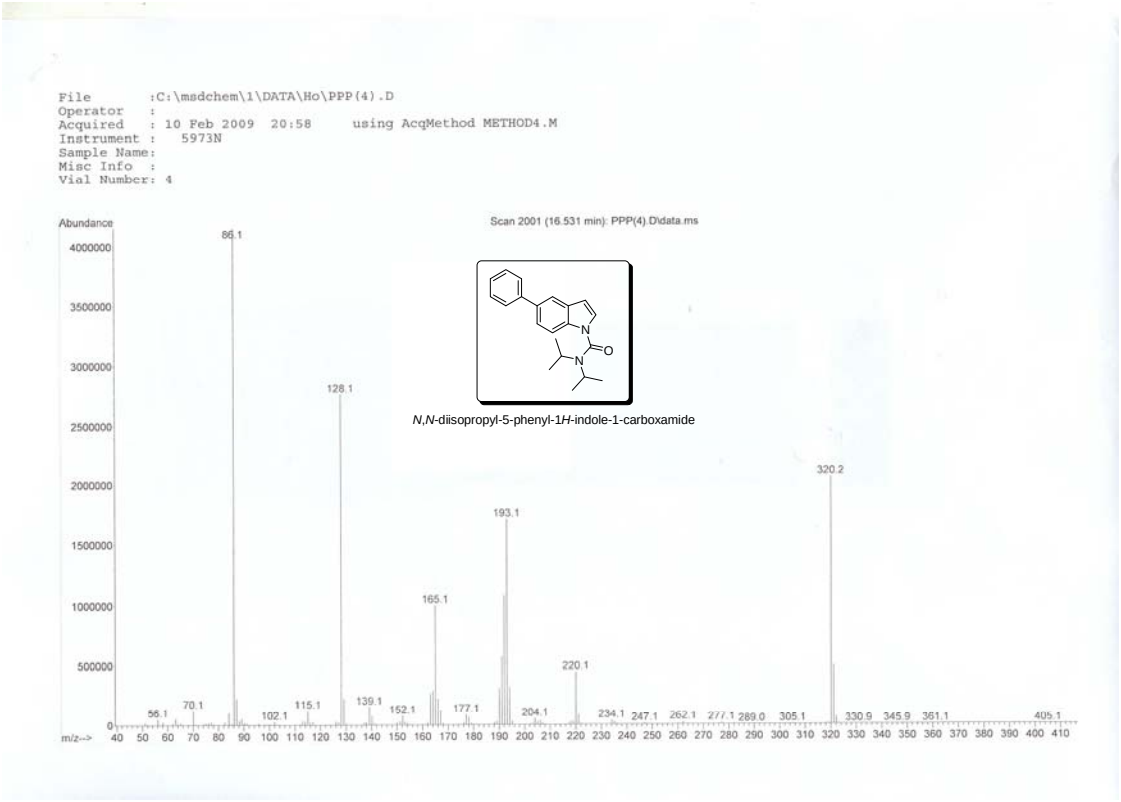
^{1}H NMR of *N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide



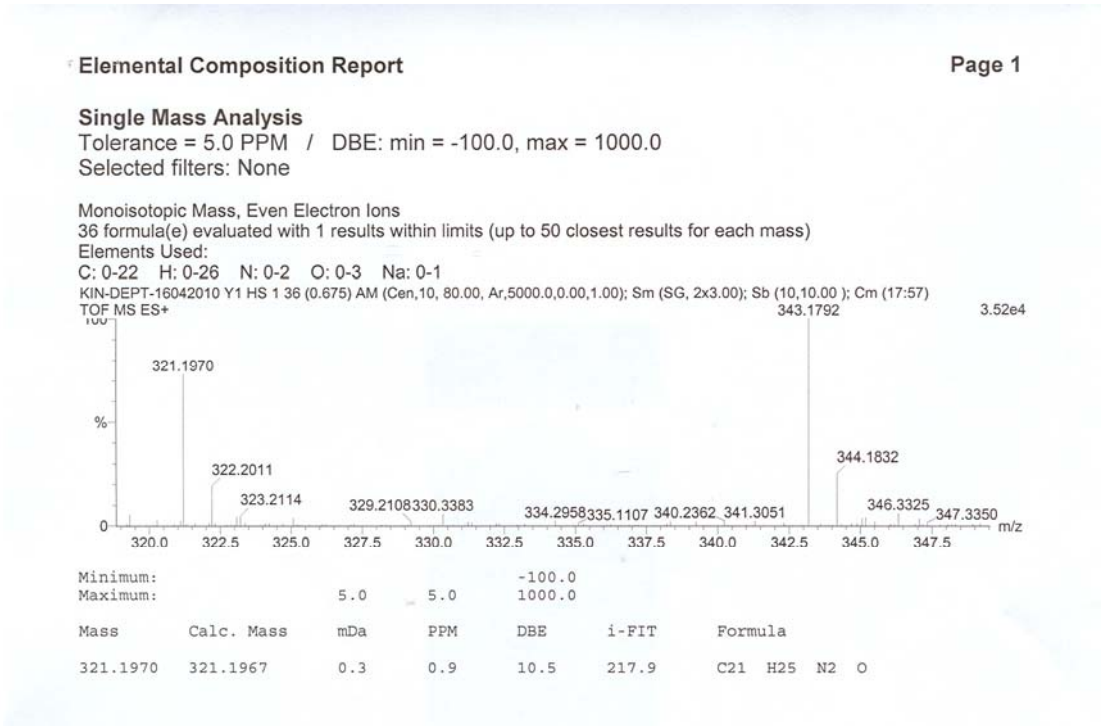
^{13}C NMR of *N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide



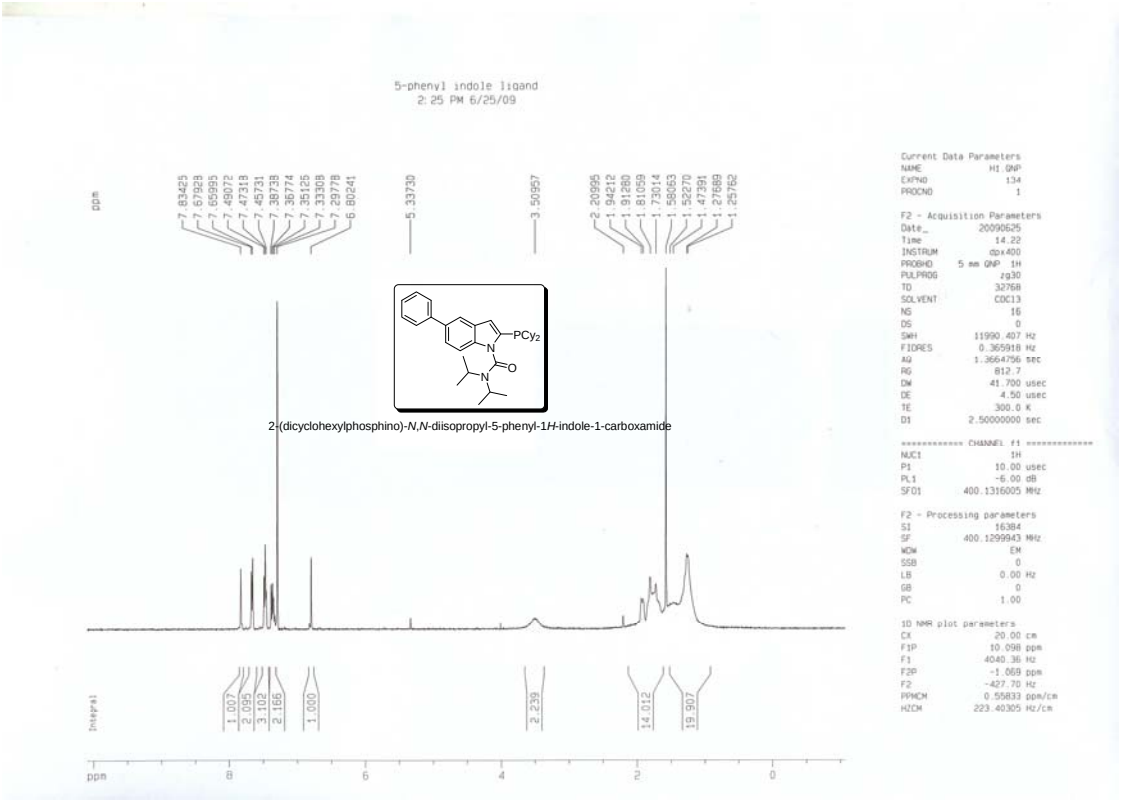
Mass spectrum of *N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide



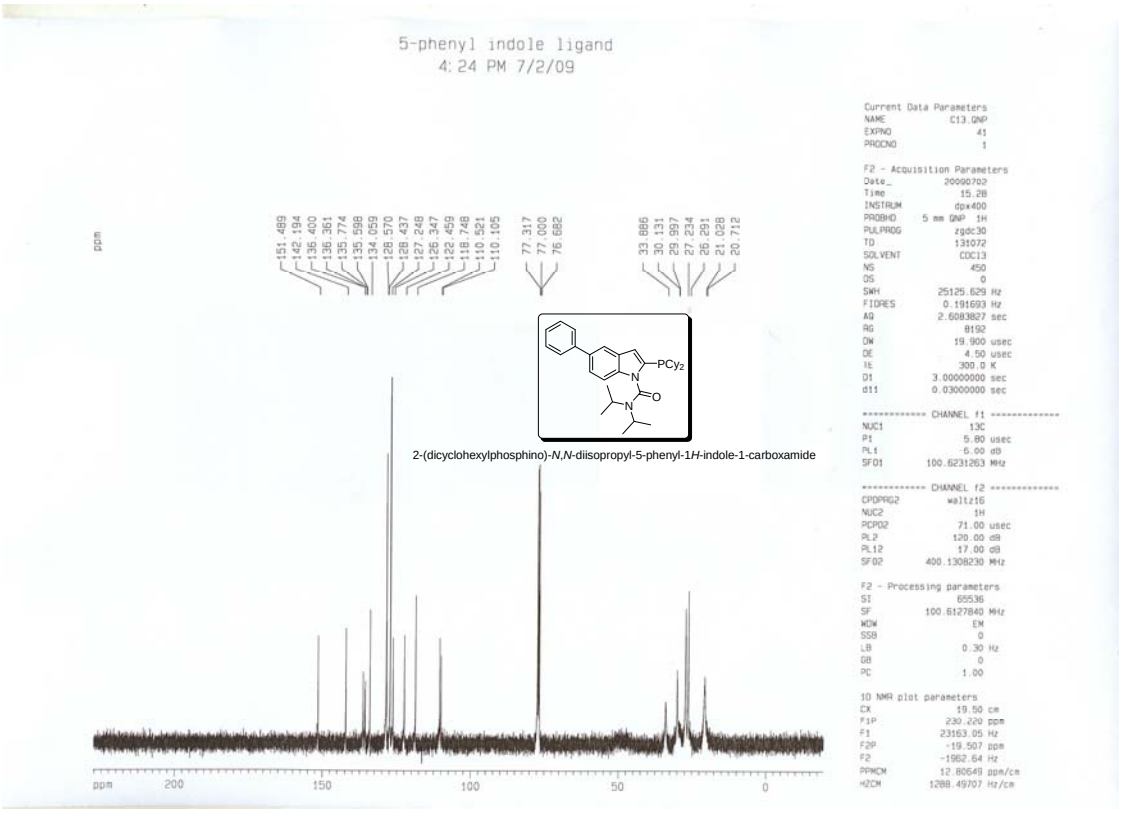
High resolution mass spectrum of *N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide



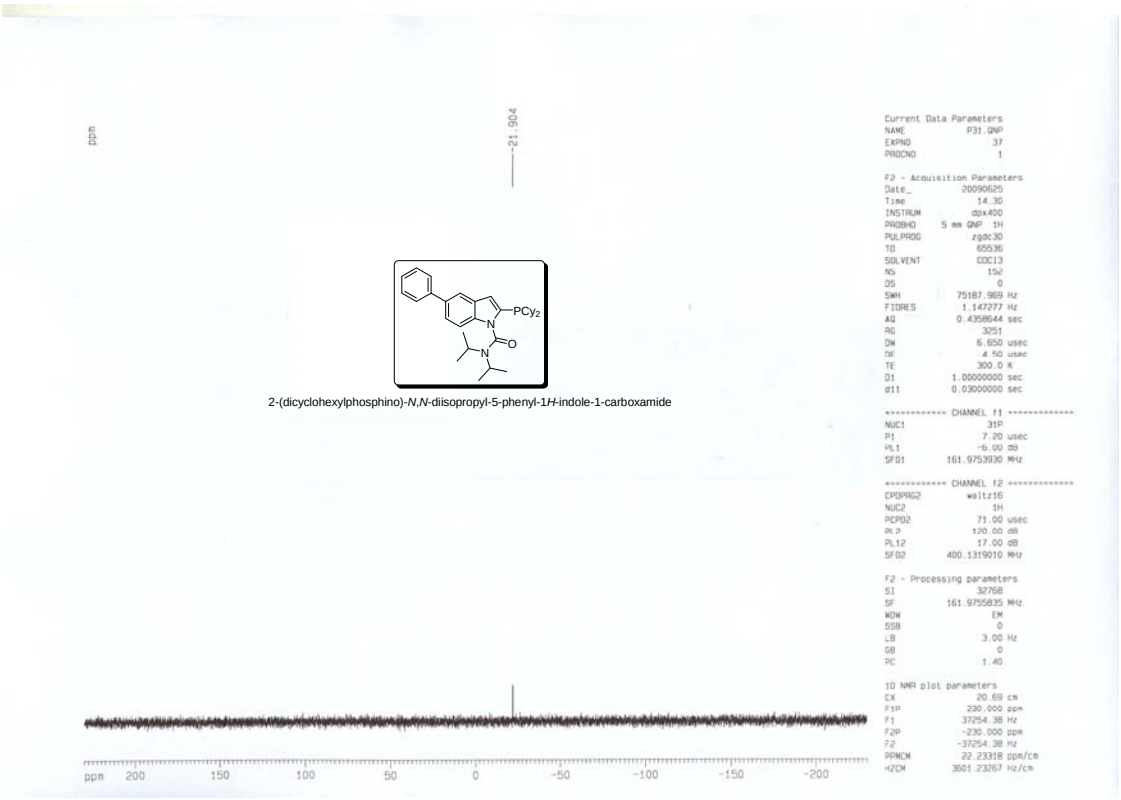
^{1}H NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide



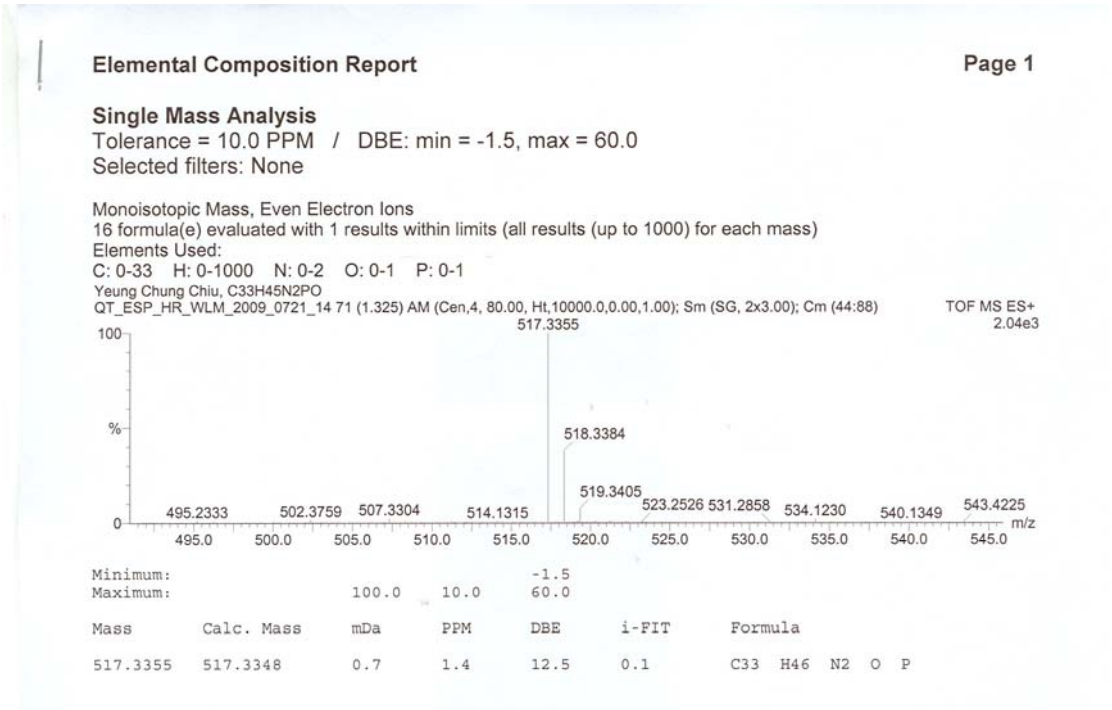
^{13}C NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide



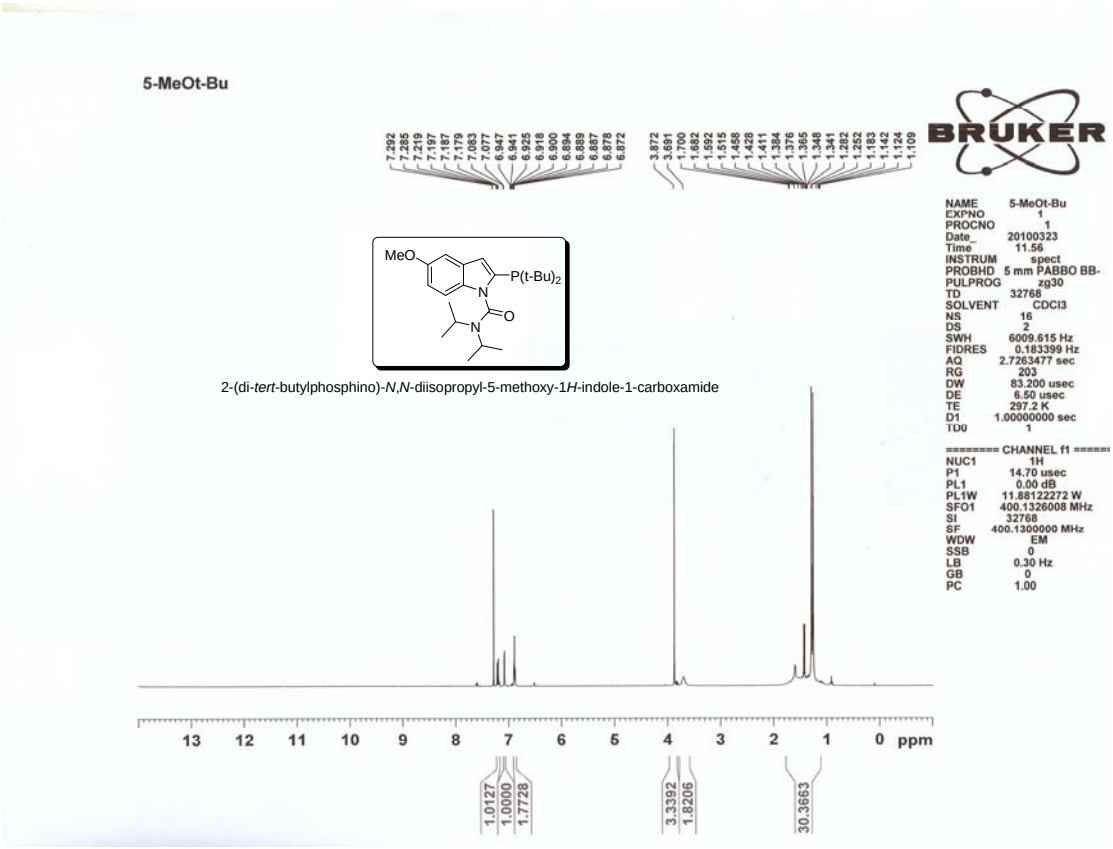
^{31}P NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide



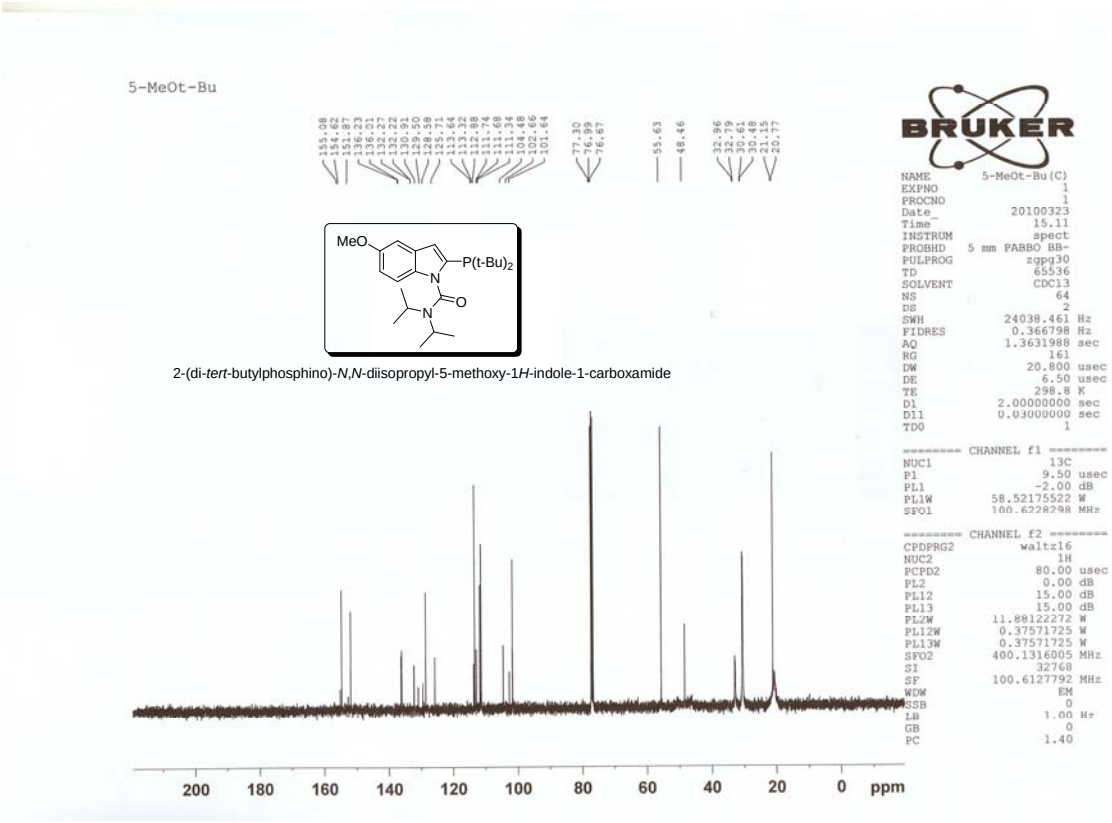
High resolution mass spectrum of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5-phenyl-1H-indole-1-carboxamide



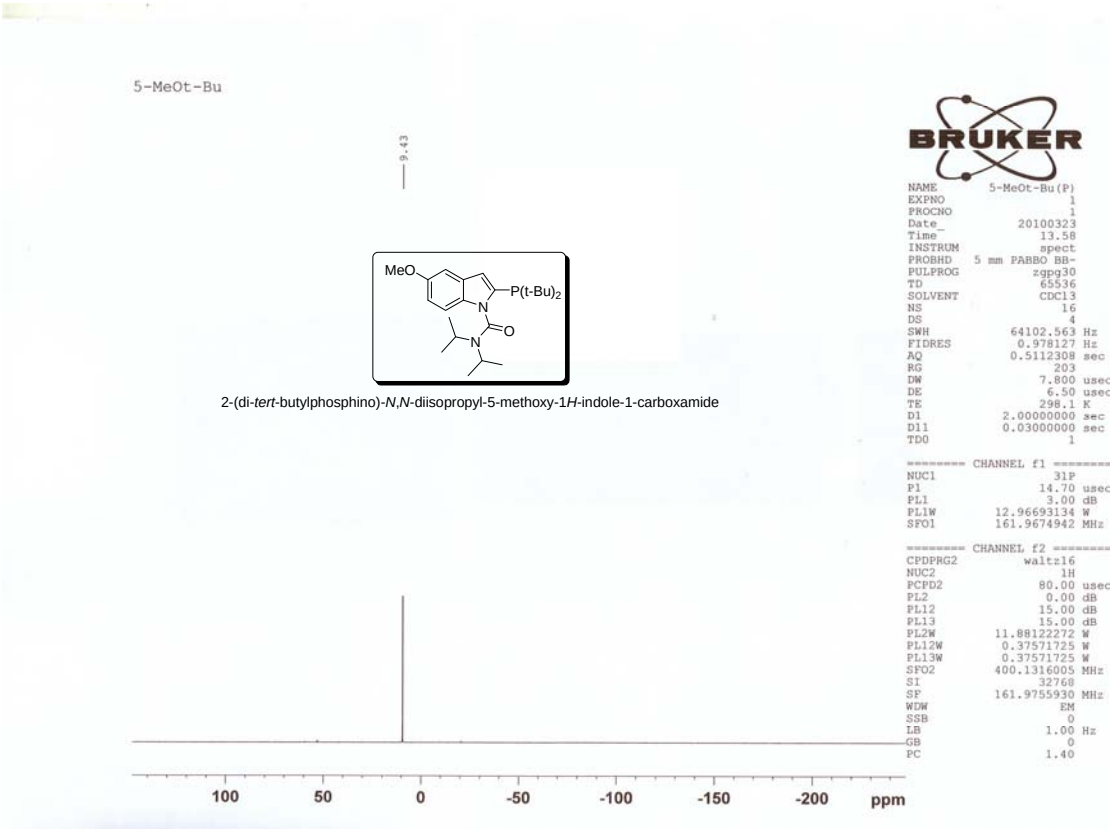
^{1}H NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



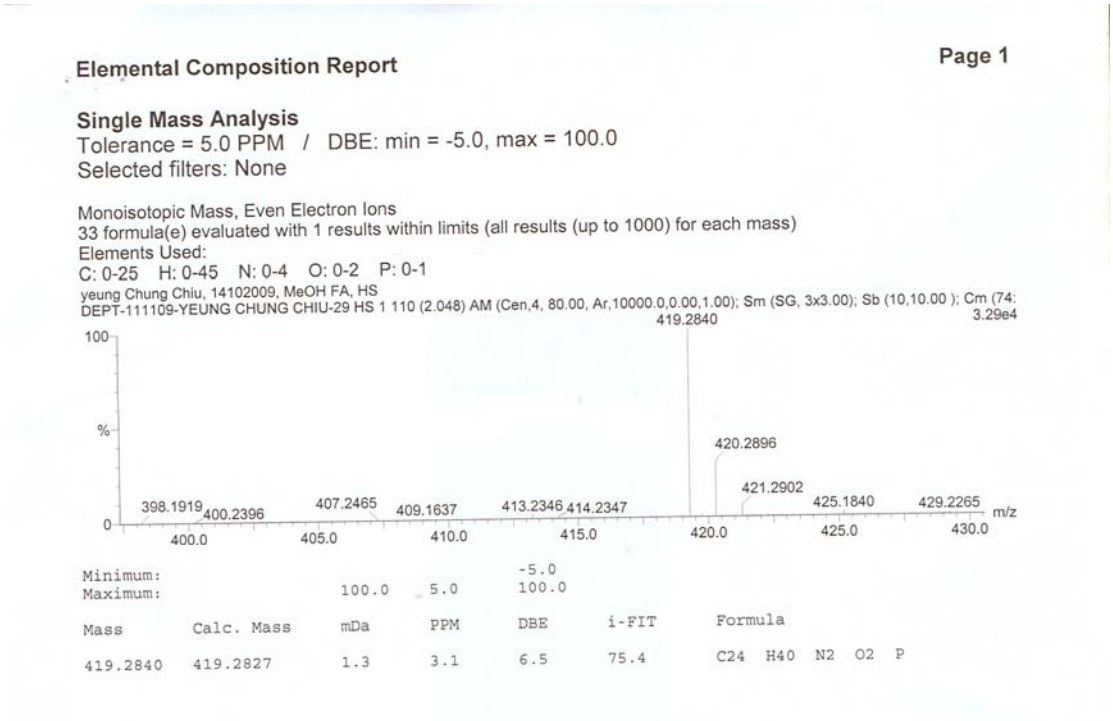
^{13}C NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



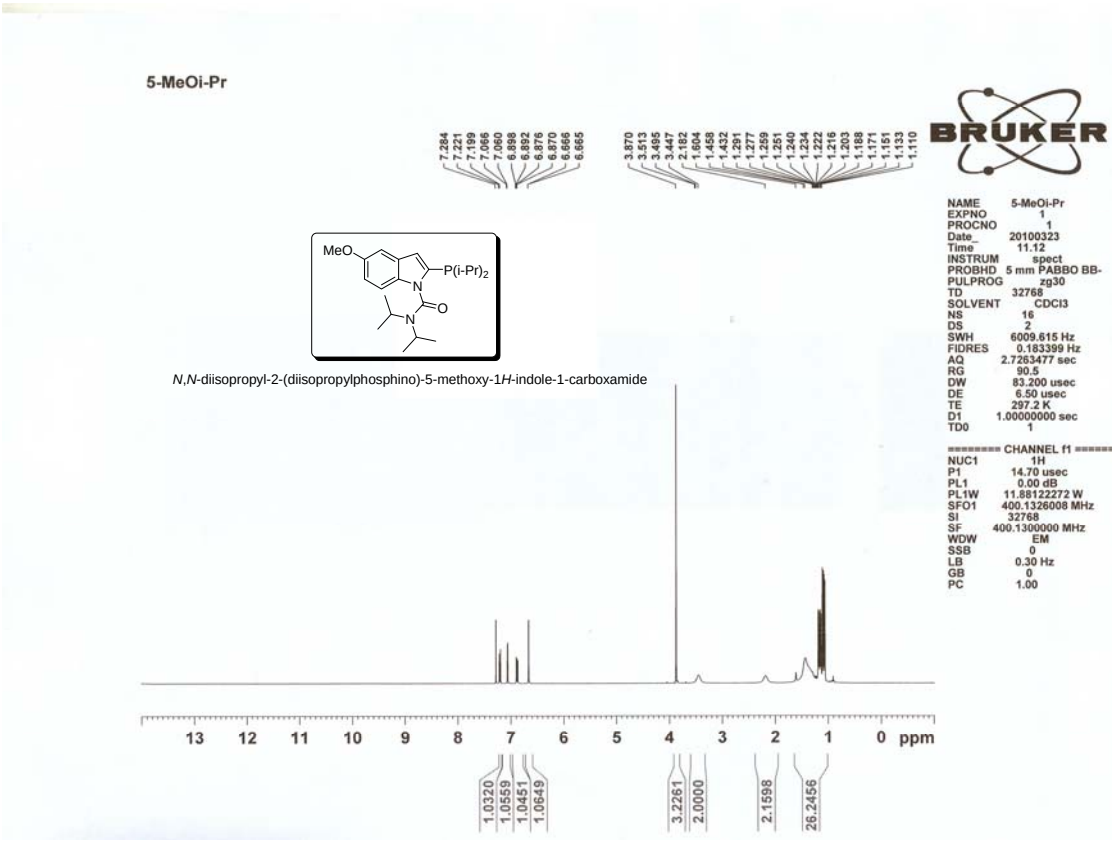
^{31}P NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



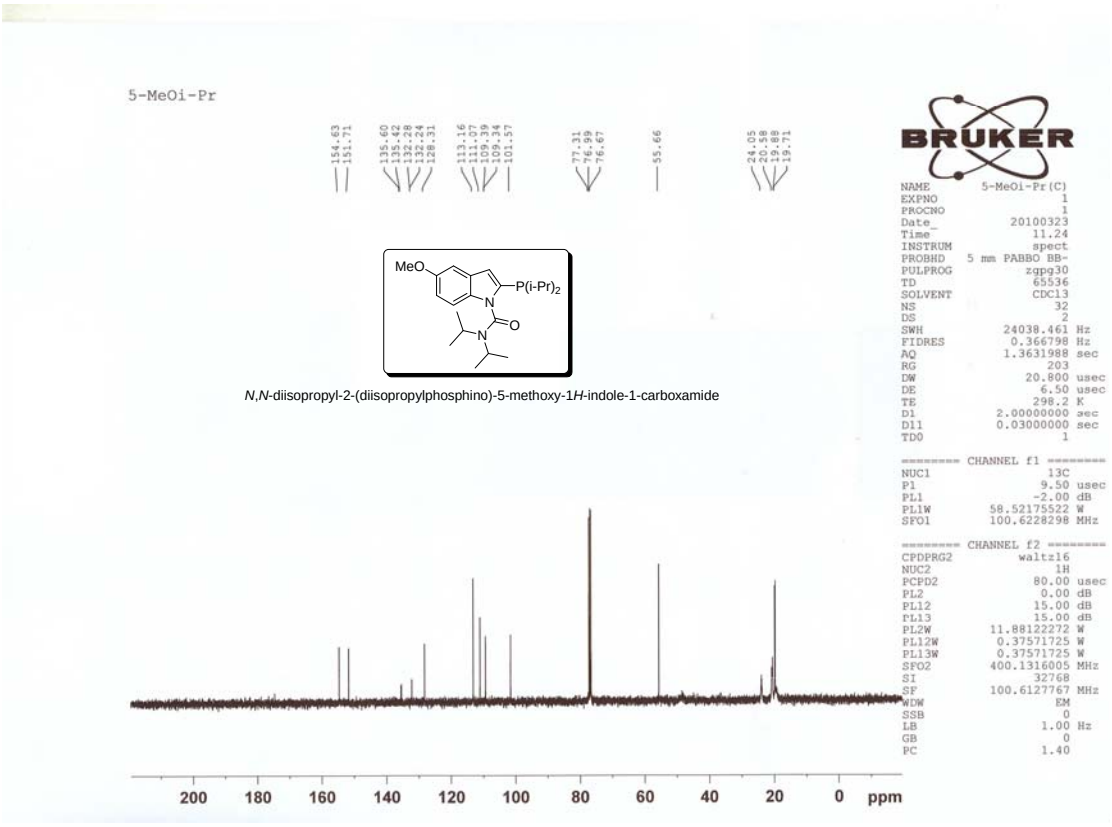
High resolution mass spectrum of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5-methoxy-1H-indole-1-carboxamide



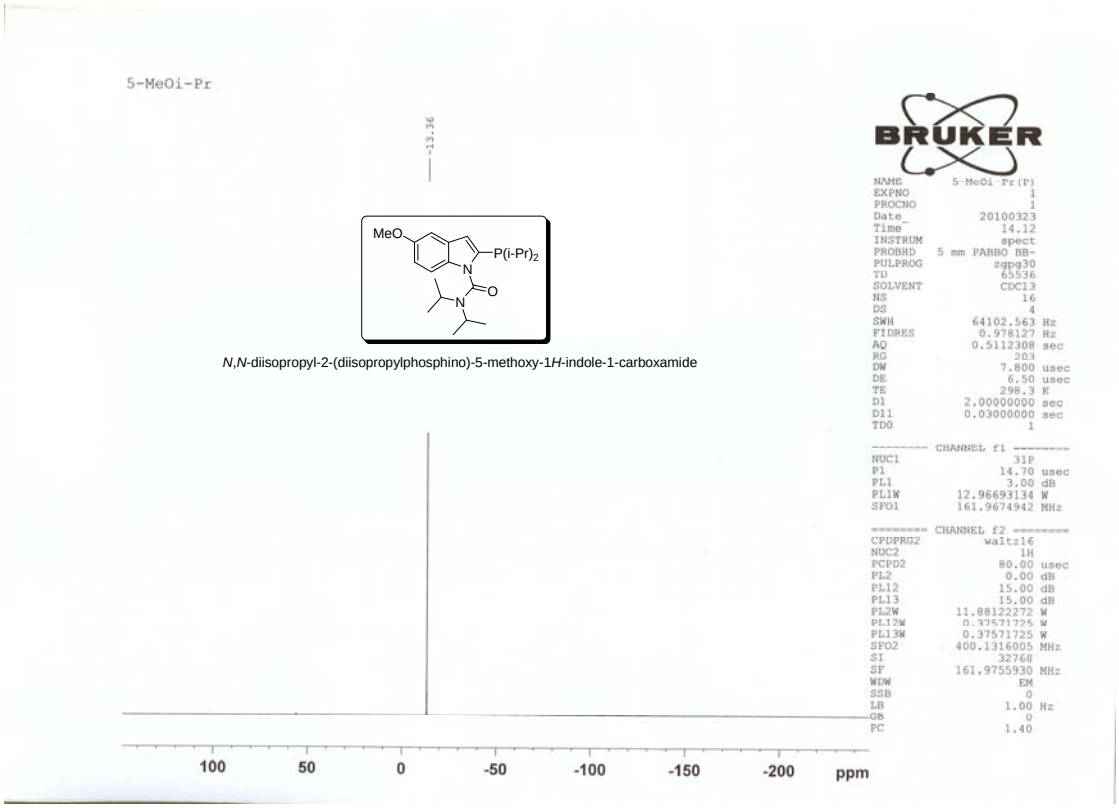
^{1}H NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide



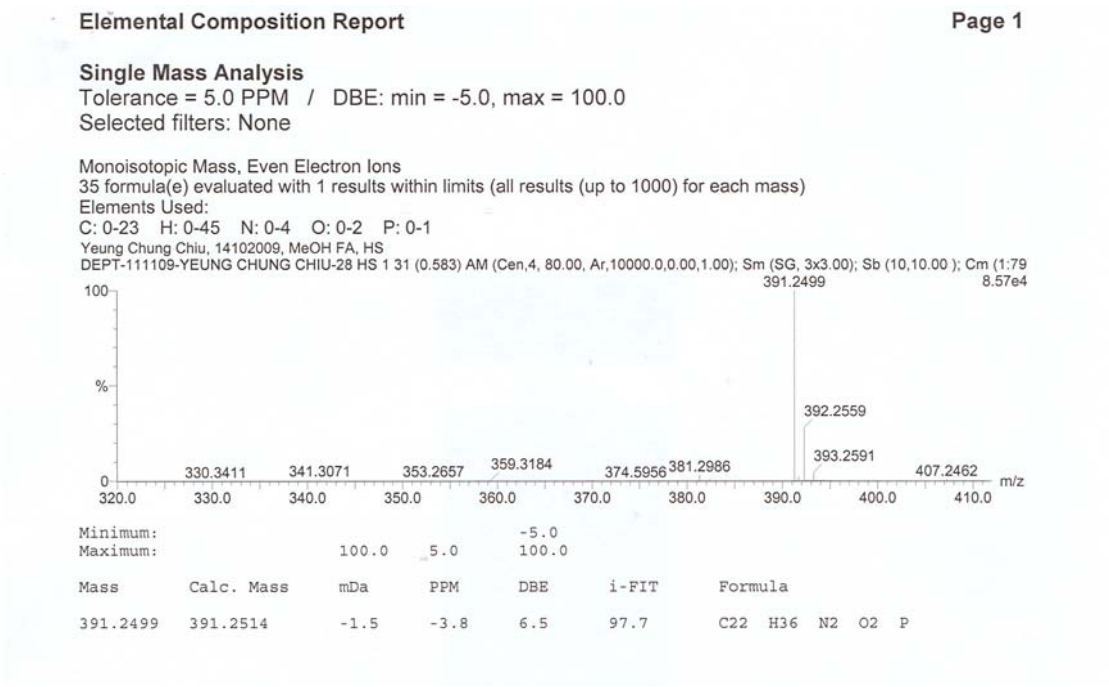
^{13}C NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide



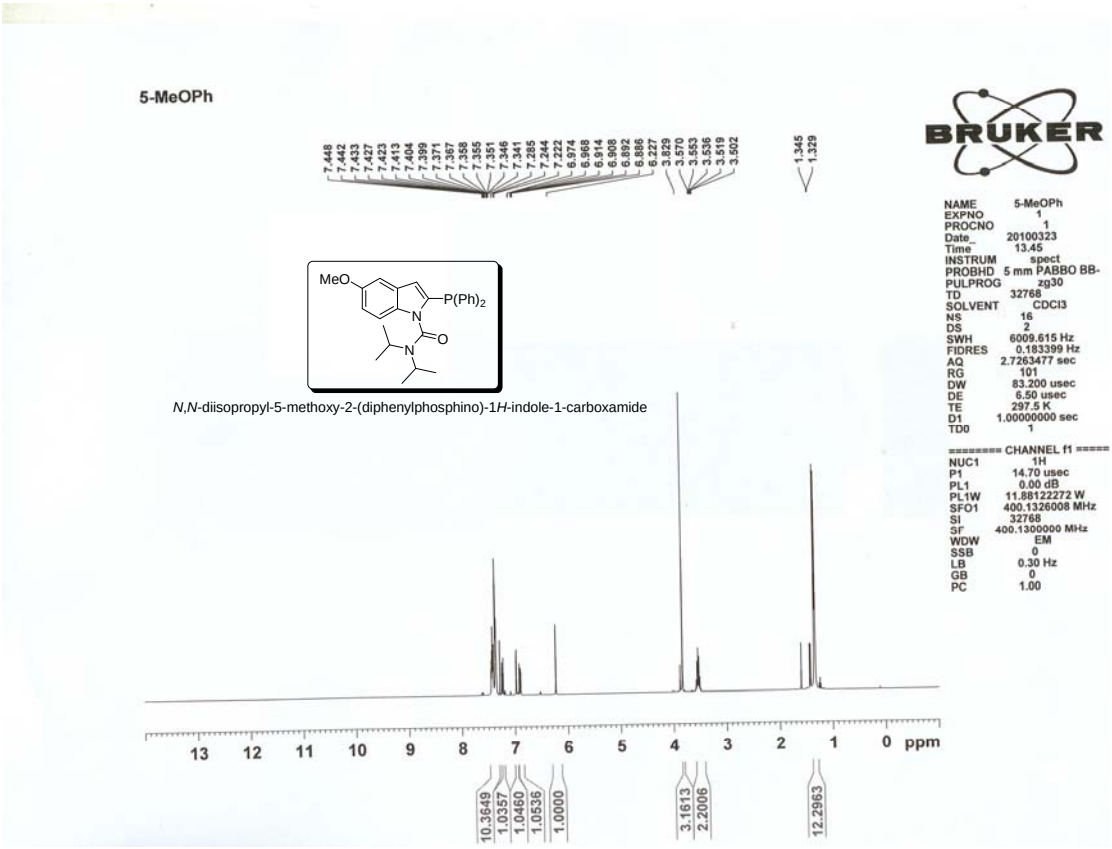
^{31}P NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide



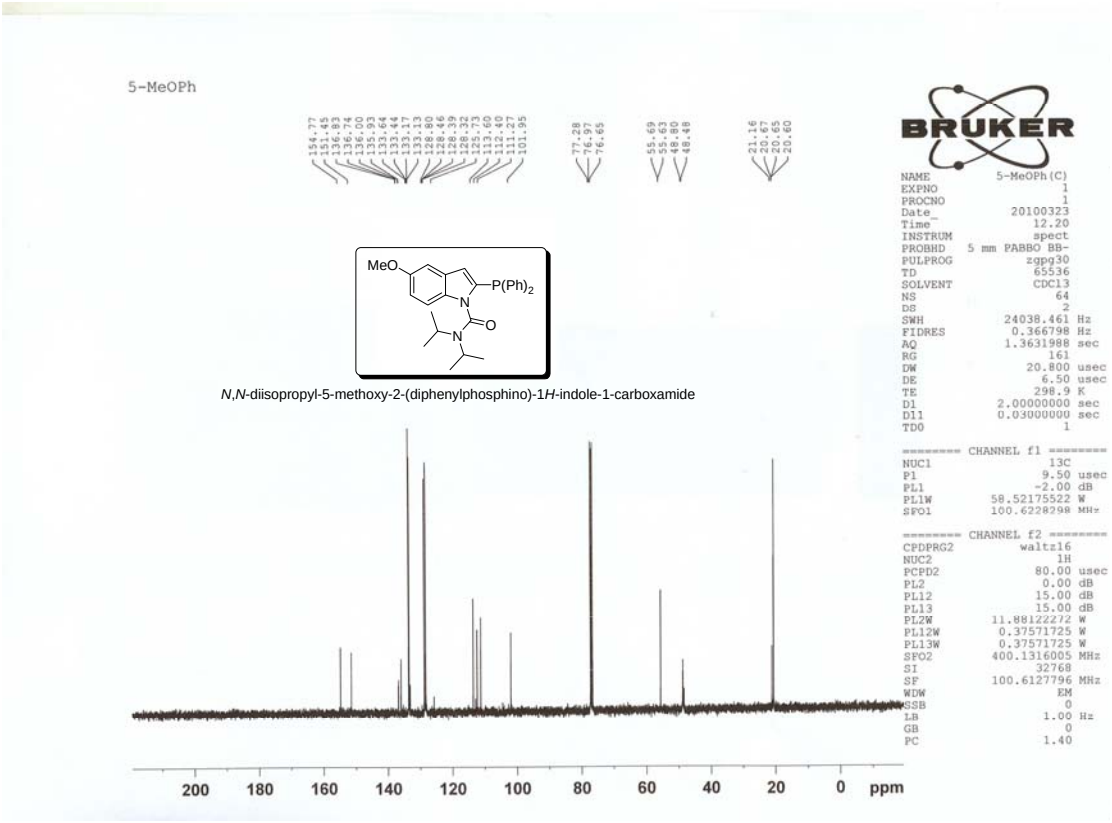
High resolution mass spectrum of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide



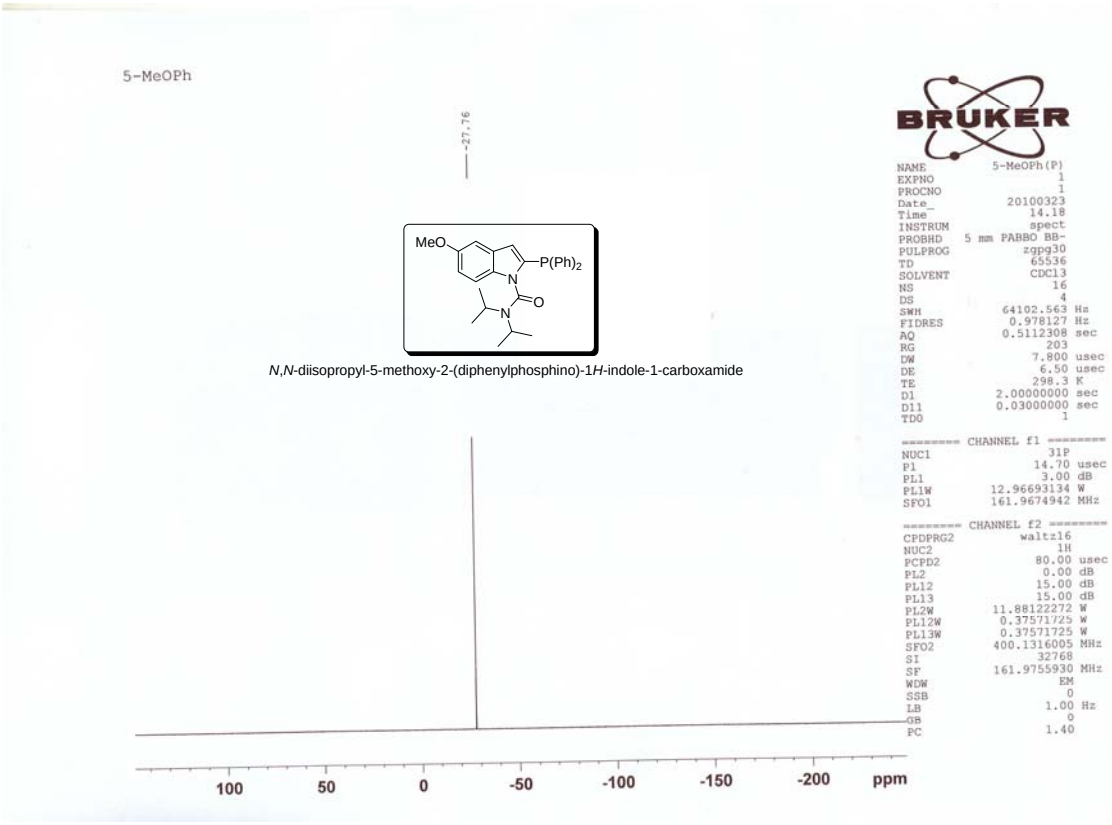
^{1}H NMR of *N*,*N*-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide



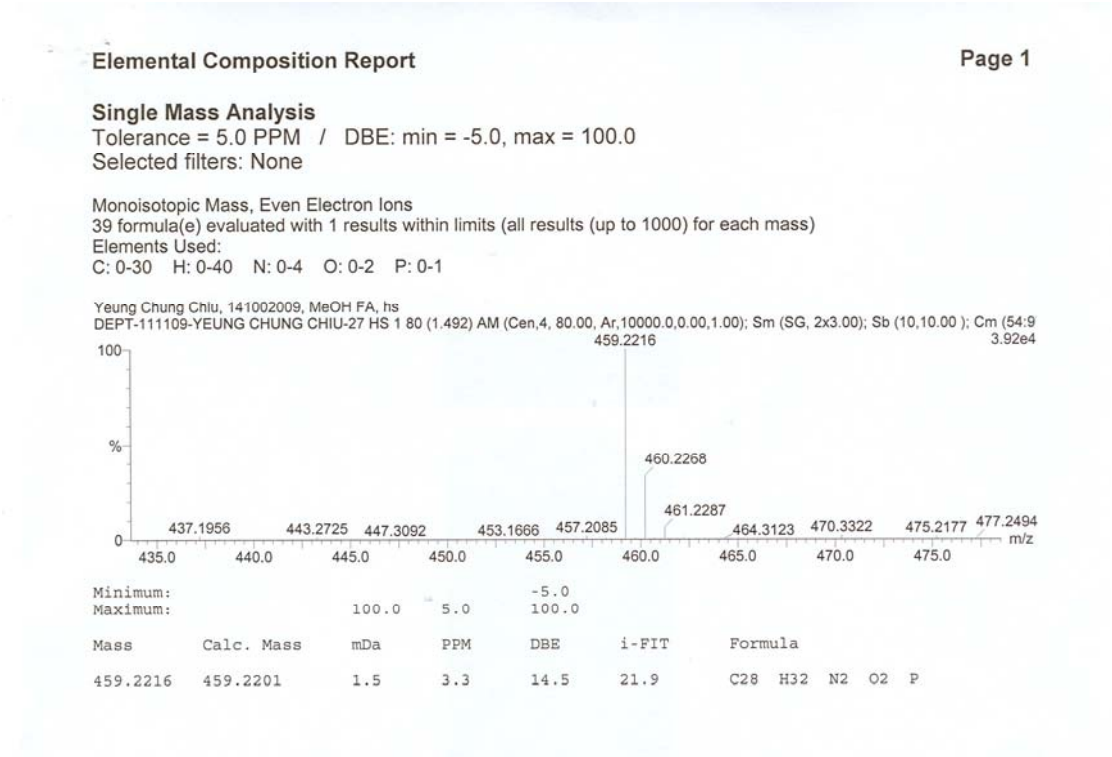
^{13}C NMR of *N*,*N*-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide



^{31}P NMR of *N*,*N*-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide

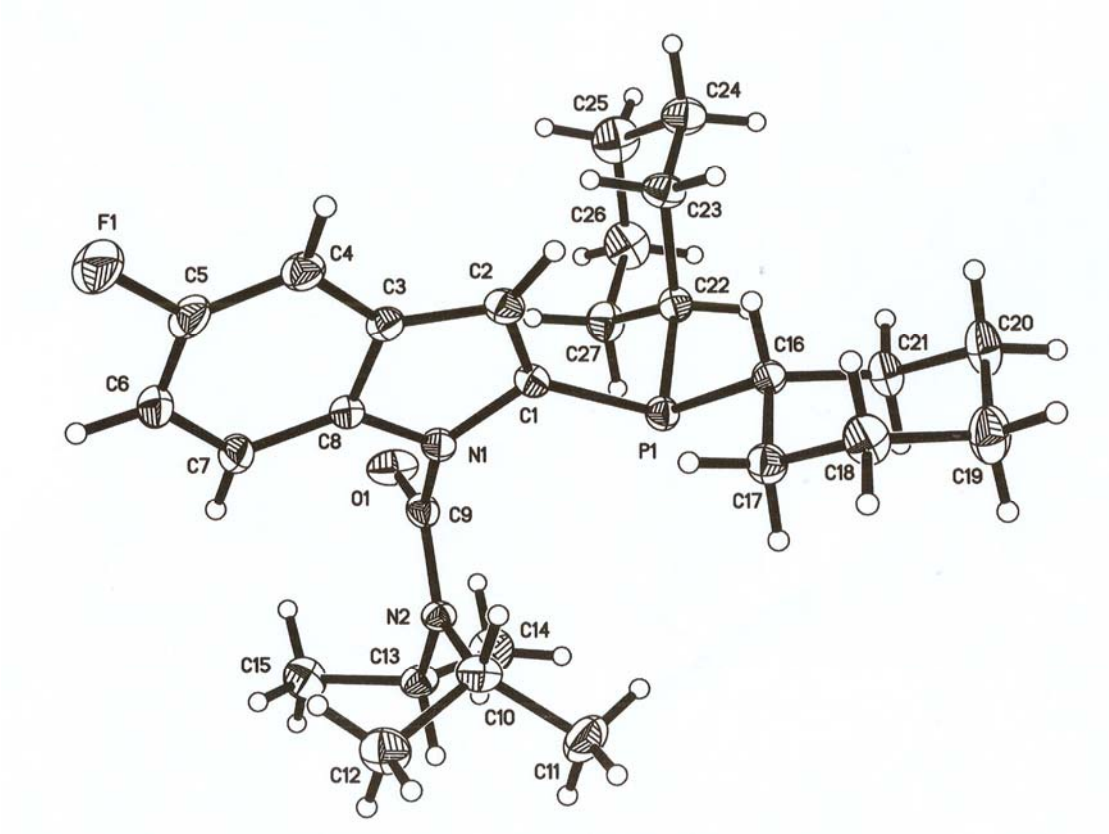


High resolution mass spectrum of *N*,*N*-diisopropyl-5-methoxy-2-(diphenylphosphino)-1H-indole-1-carboxamide



Chapter 2: X-Ray structure of ligands

X-Ray structure of 1-(2-(dicyclohexylphosphino)-5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one



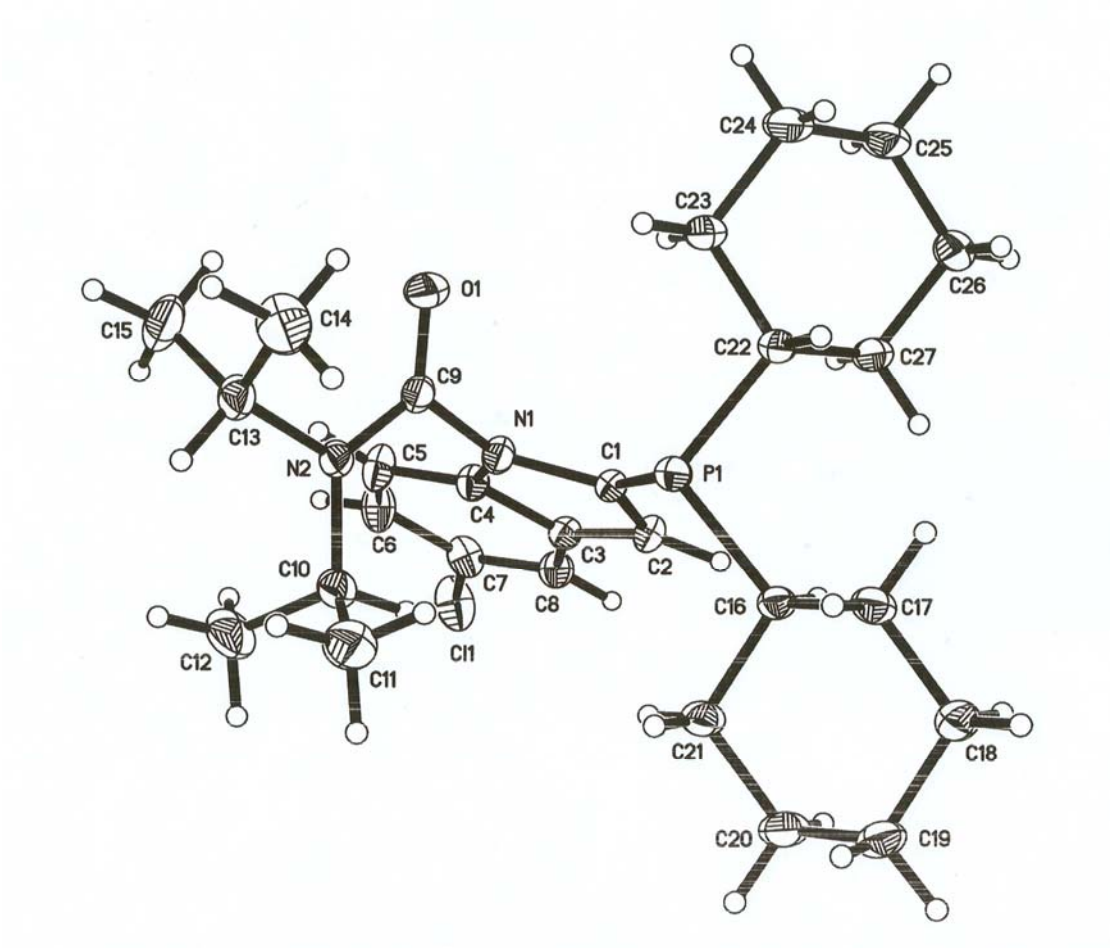
X-Ray data of 1-(2-(dicyclohexylphosphino)-5-fluoro-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one

Table 1. Crystal data and structure refinement for BCYCC13 (24 Aug 2009).

Identification code	ycc13	
Empirical formula	C_{27} H_{40} F N_2 O P	
Formula weight	458.58	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 20.2705(13) Å	α= 90°.
	b = 11.0357(6) Å	β= 90°.
	c = 11.7327(6) Å	γ = 90°.
Volume	2624.6(3) $Å^3$	
Z	4	
Density (calculated)	1.161 Mg/m^3	
Absorption coefficient	0.132 mm^{-1}	
F(000)	992	
Crystal size	0.20 x 0.16 x 0.12 mm^3	
Theta range for data collection	2.01 to 27.41°.	
Index ranges	-26<=h<=23, -14<=k<=11, -11<=l<=15	
Reflections collected	17164	
Independent reflections	5155 [R(int) = 0.1006]	
Completeness to theta = 27.41°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9843 and 0.9740	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5155 / 1 / 289	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2sigma(I)]	R1 = 0.0556, wR2 = 0.0693	
R indices (all data)	R1 = 0.1518, wR2 = 0.0879	
Absolute structure parameter	0.00	
Largest diff. peak and hole	0.198 and -0.235 $e.Å^{-3}$	

1

X-Ray structure of 1-(5-chloro-2-(dicyclohexylphosphino)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one



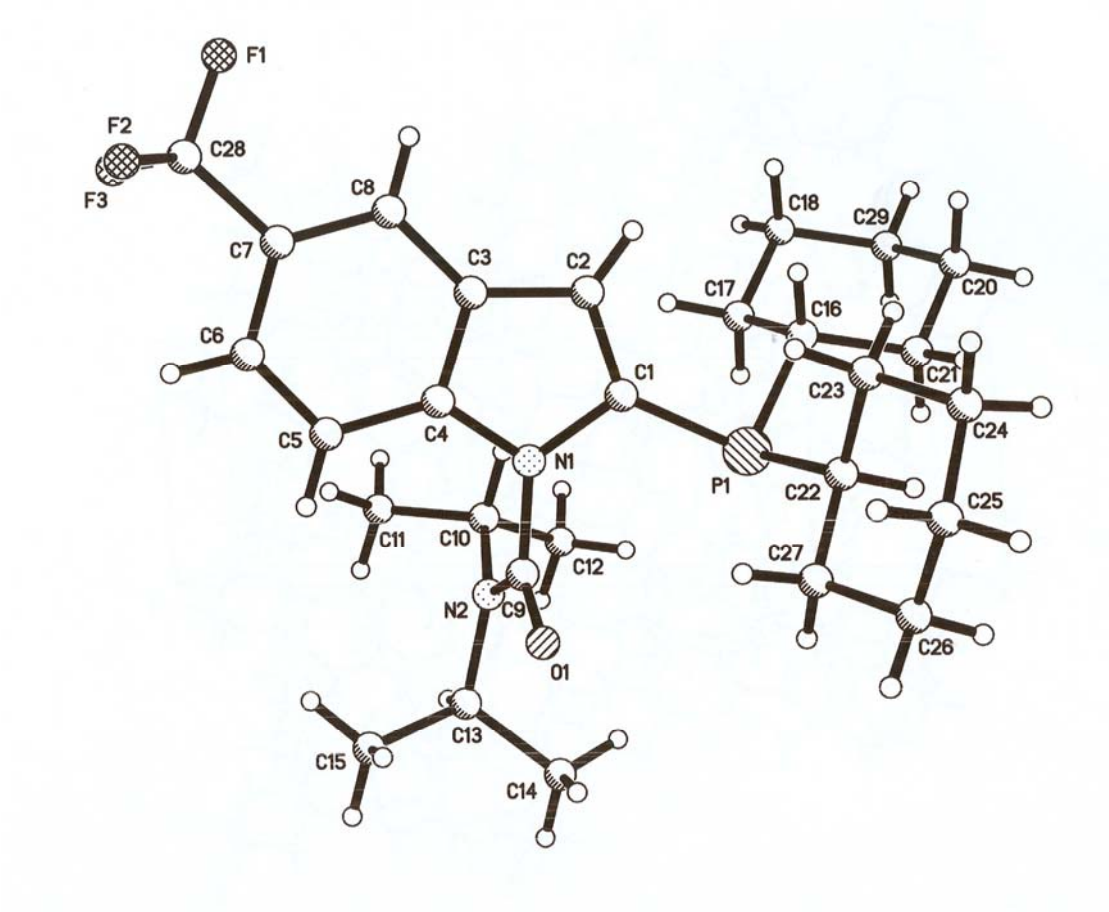
X-Ray data of 1-(5-chloro-2-(dicyclohexylphosphino)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one

Table 1. Crystal data and structure refinement for BCYCC2 (27 May 2009).

Identification code	ycc2	
Empirical formula	$C_{27}H_{40}N_2OPCl$	
Formula weight	475.03	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6643(2) Å	α= 96.526(2)°.
	b = 8.1492(2) Å	β= 92.228(2)°.
	c = 22.0029(5) Å	γ = 95.727(2)°.
Volume	1356.78(6) $Å^3$	
Z	2	
Density (calculated)	1.163 Mg/m^3	
Absorption coefficient	0.220 mm^{-1}	
F(000)	512	
Crystal size	0.40 x 0.40 x 0.38 mm^3	
Theta range for data collection	0.93 to 27.60°.	
Index ranges	-9<=h<=9, -10<=k<=10, -28<=l<=28	
Reflections collected	36558	
Independent reflections	6156 [R(int) = 0.1909]	
Completeness to theta = 27.60°	97.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.789	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6156 / 0 / 293	
Goodness-of-fit on F^2	1.003	
Final R indices [I>2sigma(I)]	R1 = 0.0548, wR2 = 0.1041	
R indices (all data)	R1 = 0.2922, wR2 = 0.1290	
Largest diff. peak and hole	0.210 and -0.171 $e.Å^{-3}$	

1

X-Ray structure of 1-(2-(dicyclohexylphosphino)-5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one



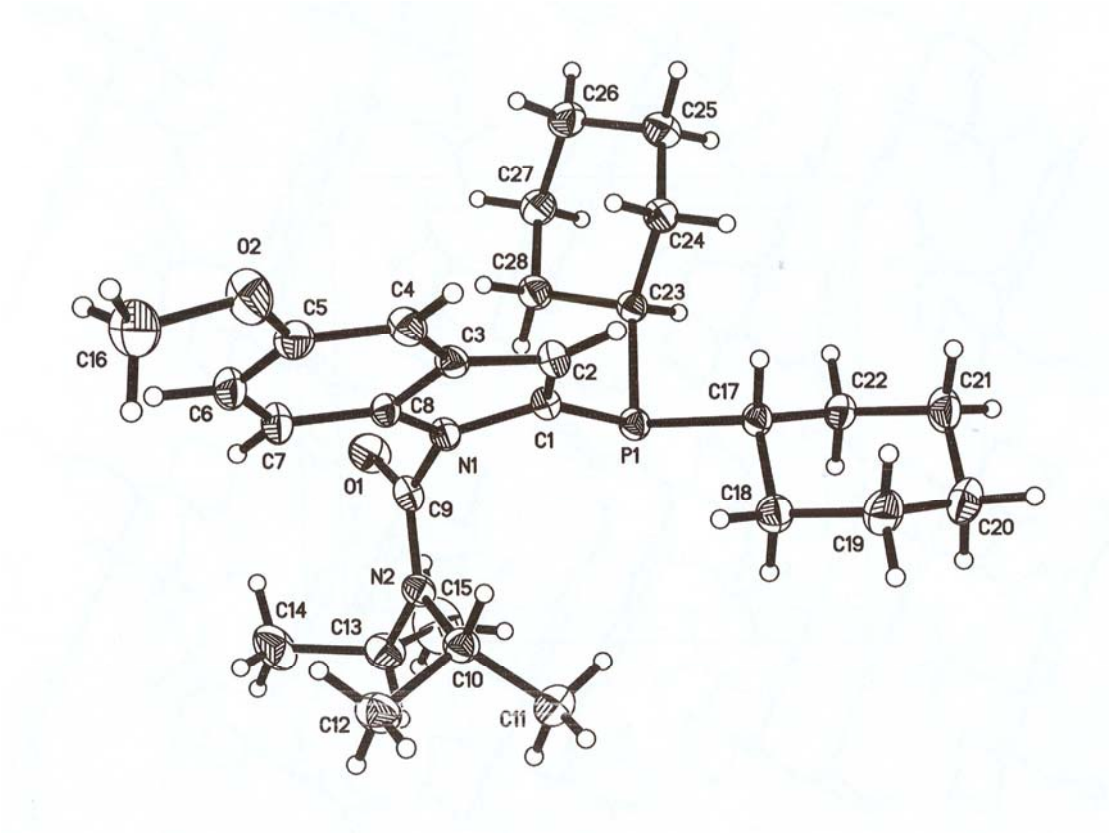
X-Ray data of 1-(2-(dicyclohexylphosphino)-5-(trifluoromethyl)-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one

Table 1. Crystal data and structure refinement for BCYCC1 (26 May 2009).

Identification code	ycc1	
Empirical formula	C_{28} H_{40} F_3 N_2 O P	
Formula weight	508.59	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.6284(2) Å	α= 90°.
	b = 14.7521(3) Å	β= 95.343(2)°.
	c = 25.1897(6) Å	γ = 90°.
Volume	2822.40(12) Å^3	
Z	4	
Density (calculated)	1.197 Mg/m^3	
Absorption coefficient	0.139 mm^{-1}	
F(000)	1088	
Crystal size	0.40 x 0.34 x 0.30 mm^3	
Theta range for data collection	1.60 to 27.34°.	
Index ranges	-9<=h<=9, -18<=k<=18, -32<=l<=32	
Reflections collected	35867	
Independent reflections	6350 [R(int) = 0.1029]	
Completeness to theta = 27.34°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.836	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6350 / 12 / 349	
Goodness-of-fit on F^2	1.004	
Final R indices [I>2sigma(I)]	R1 = 0.0682, wR2 = 0.1676	
R indices (all data)	R1 = 0.1641, wR2 = 0.2141	
Largest diff. peak and hole	0.524 and -0.259 e.Å^{-3}	

1

X-Ray structure of 1-(2-(dicyclohexylphosphino)-5-methoxy-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one



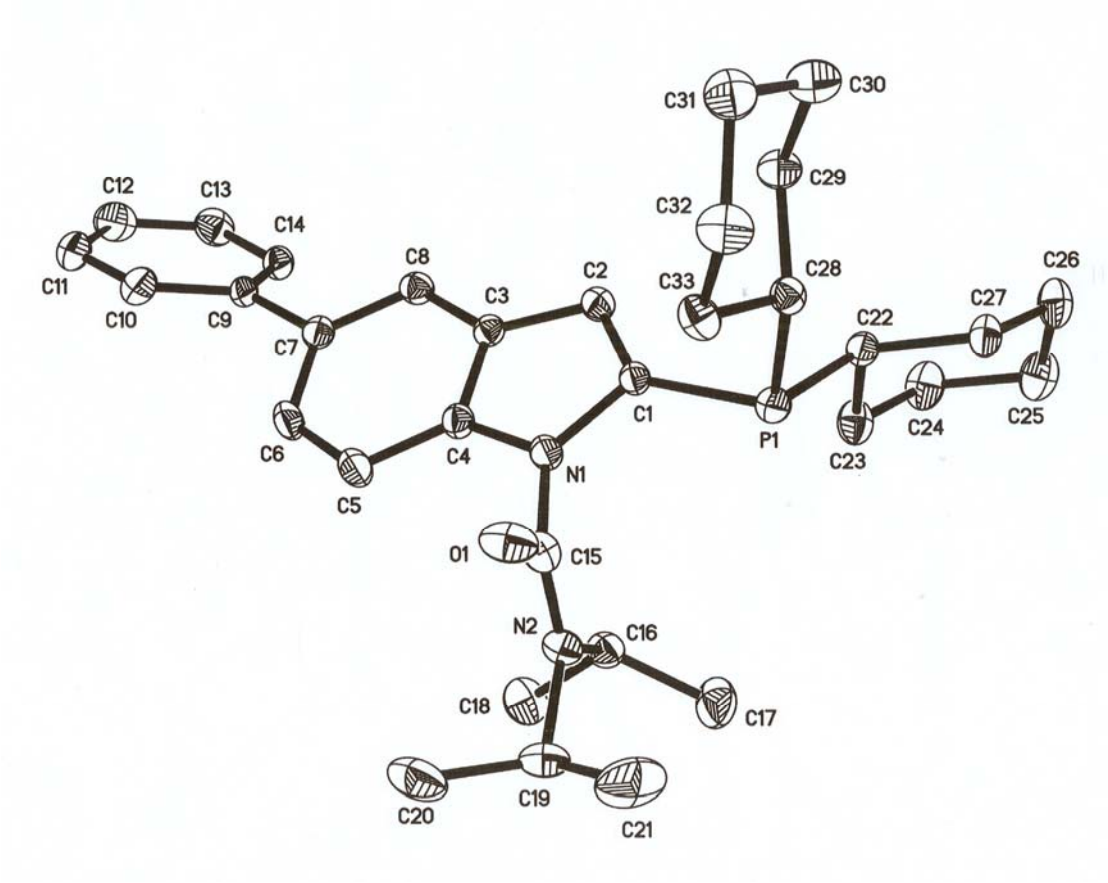
X-Ray data of 1-(2-(dicyclohexylphosphino)-5-methoxy-1H-indol-1-yl)-2-isopropyl-3-methylbutan-1-one

Table 1. Crystal data and structure refinement for BCYCC17 (8 Oct 2009).

Identification code	ycc17	
Empirical formula	$C_{28}H_{43}N_2O_2P$	
Formula weight	470.61	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 13.8715(4) Å	α= 90°.
	b = 12.0586(4) Å	β= 92.343(3)°.
	c = 16.4889(7) Å	γ = 90°.
Volume	2755.81(17) Å^3	
Z	4	
Density (calculated)	1.134 Mg/m^3	
Absorption coefficient	0.125 mm^{-1}	
F(000)	1024	
Crystal size	0.26 x 0.26 x 0.20 mm^3	
Theta range for data collection	2.09 to 27.50°.	
Index ranges	-18<=h<=15, -15<=k<=13, -19<=l<=21	
Reflections collected	19921	
Independent reflections	6320 [R(int) = 0.1197]	
Completeness to theta = 27.50°	99.8 %	
Absorption correction	Nulti-scan	
Max. and min. transmission	0.9754 and 0.9682	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6320 / 0 / 298	
Goodness-of-fit on F^2	0.993	
Final R indices [I>2sigma(I)]	R1 = 0.0658, wR2 = 0.0788	
R indices (all data)	R1 = 0.2157, wR2 = 0.1035	
Largest diff. peak and hole	0.199 and -0.190 e.Å^{-3}	

1

X-Ray structure of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide



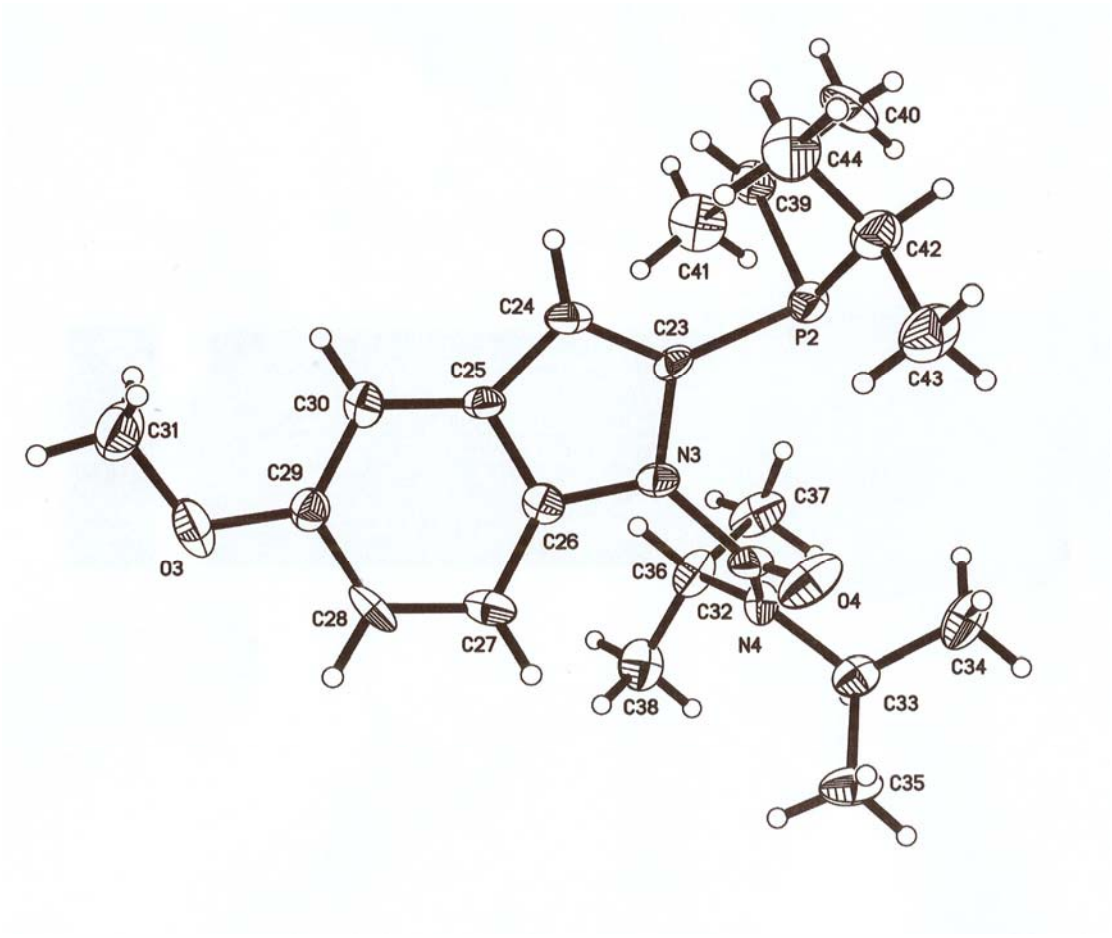
X-Ray data of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5-phenyl-1H-indole-1-carboxamide

Table 1. Crystal data and structure refinement for BCYCC9 (6 Aug 2009).

Identification code	ycc9	
Empirical formula	C_{33} H_{45} N_2 O P	
Formula weight	516.68	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 34.0668(14) Å	α= 90°.
	b = 8.0051(3) Å	β= 126.475(2)°.
	c = 27.0907(11) Å	γ = 90°.
Volume	5940.7(4) $Å^3$	
Z	8	
Density (calculated)	1.155 Mg/m^3	
Absorption coefficient	0.120 mm^{-1}	
F(000)	2240	
Crystal size	0.20 x 0.14 x 0.08 mm^3	
Theta range for data collection	1.87 to 27.31°.	
Index ranges	-33<=h<=43, -9<=k<=10, -34<=l<=28	
Reflections collected	20511	
Independent reflections	6633 [R(int) = 0.1242]	
Completeness to theta = 27.31°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9905 and 0.9764	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6633 / 0 / 334	
Goodness-of-fit on F^2	0.997	
Final R indices [I>2sigma(I)]	R1 = 0.0725, wR2 = 0.1077	
R indices (all data)	R1 = 0.2202, wR2 = 0.1425	
Largest diff. peak and hole	0.224 and -0.226 $e.Å^{-3}$	

1

X-Ray structure of N,N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide



X-Ray data of N,N-diisopropyl-2-(diisopropylphosphino)-5-methoxy-1H-indole-1-carboxamide

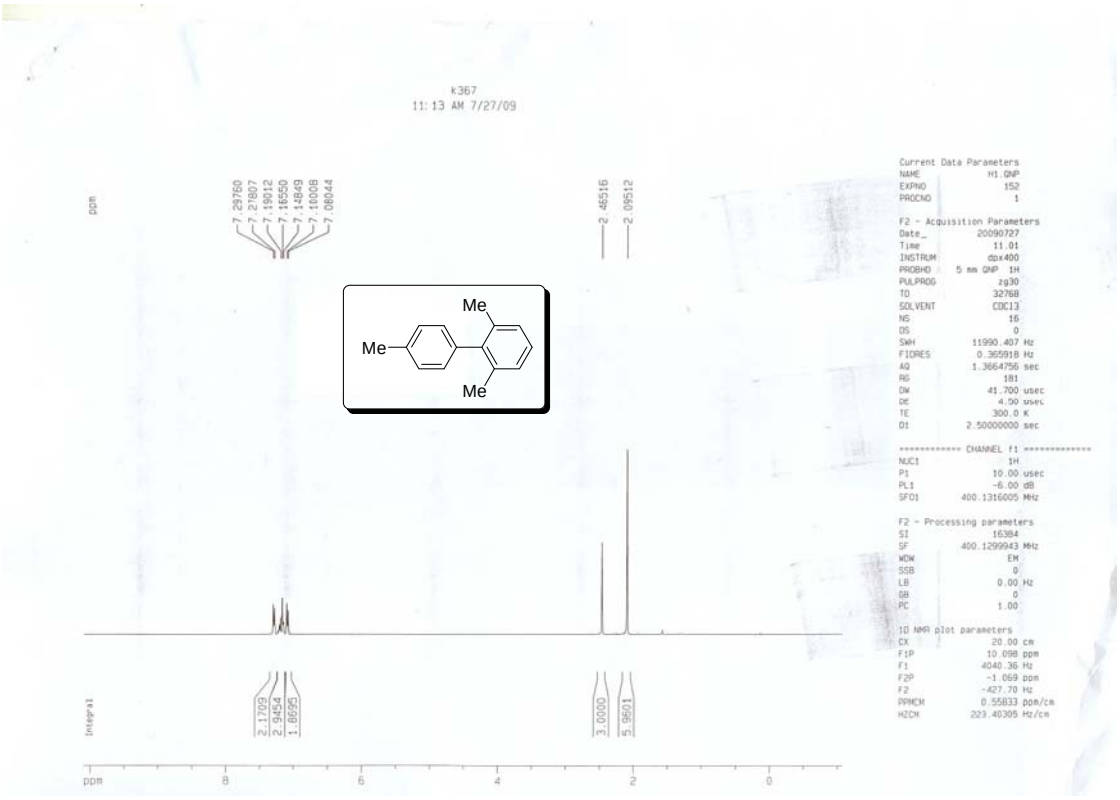
Table 1. Crystal data and structure refinement for BCYCC24 (9 Jul 2010).

Identification code	ycc24	
Empirical formula	C_{22} H_{35} N_2 O_2 P	
Formula weight	390.49	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 14.1131(8) Å	α= 90°.
	b = 15.0301(7) Å	β= 90°.
	c = 22.7013(13) Å	γ = 90°.
Volume	4815.4(4) Å^3	
Z	8	
Density (calculated)	1.077 Mg/m^3	
Absorption coefficient	0.131 mm^{-1}	
F(000)	1696	
Crystal size	0.30 x 0.20 x 0.12 mm^3	
Theta range for data collection	1.62 to 27.37°.	
Index ranges	-13<=h<=18, -19<=k<=16, -15<=l<=29	
Reflections collected	26064	
Independent reflections	10769 [R(int) = 0.1434]	
Completeness to theta = 27.37°	99.4 %	
Absorption correction	Muti-scan	
Max. and min. transmission	0.9844 and 0.9617	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10769 / 16 / 484	
Goodness-of-fit on F^2	0.900	
Final R indices [I>2sigma(I)]	R1 = 0.0831, wR2 = 0.1495	
R indices (all data)	R1 = 0.3126, wR2 = 0.2335	
Absolute structure parameter	0.4(5)	
Largest diff. peak and hole	0.183 and -0.199 e.Å^{-3}	

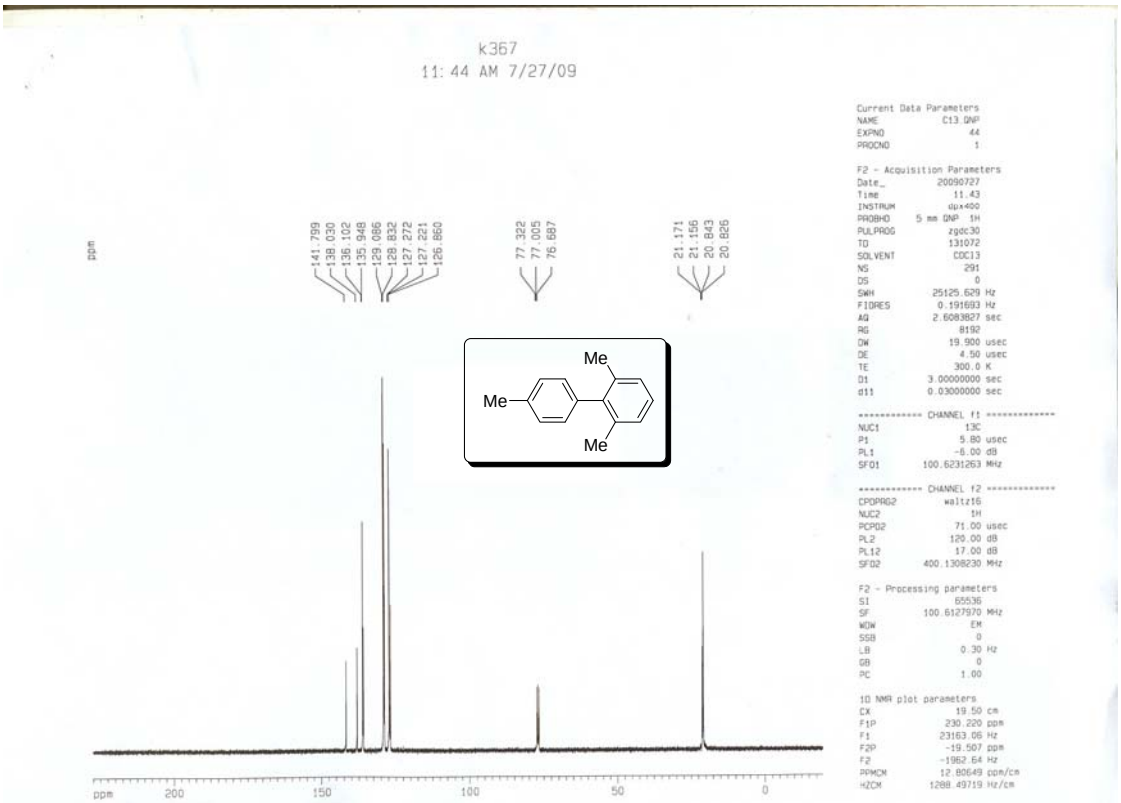
1

Chapter 2: NMR spectrum of cross-coupling products

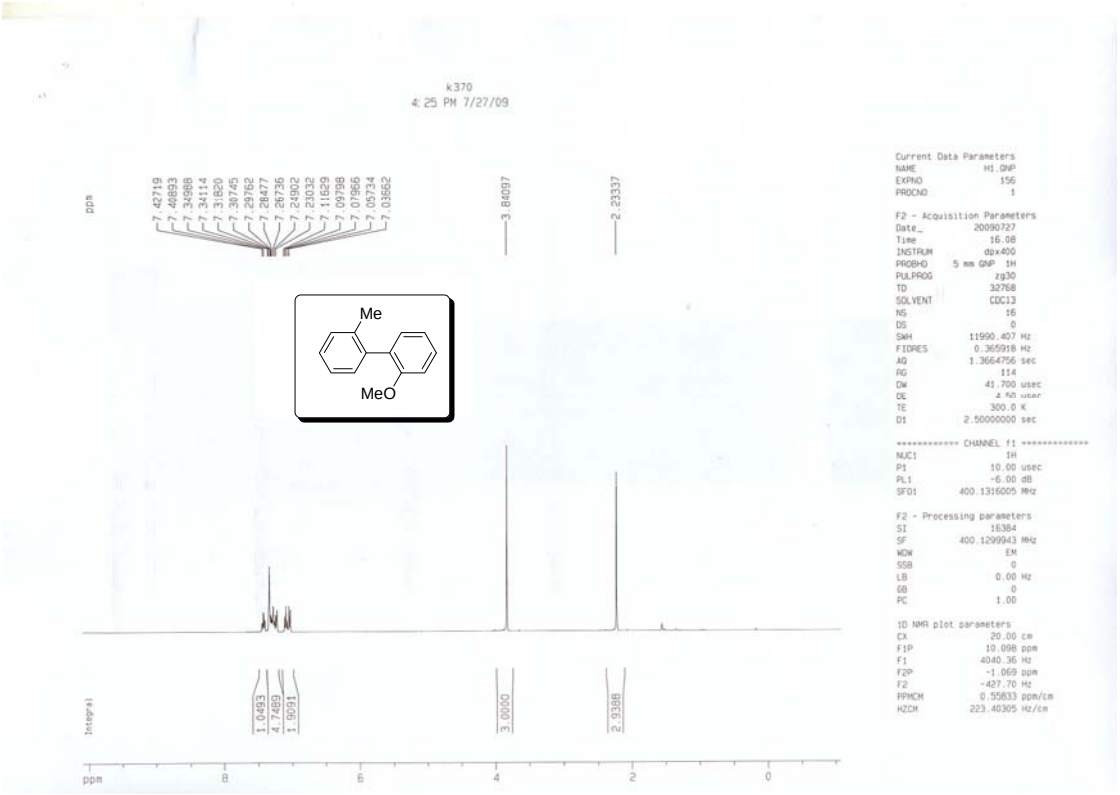
^{1}H NMR of entry 1



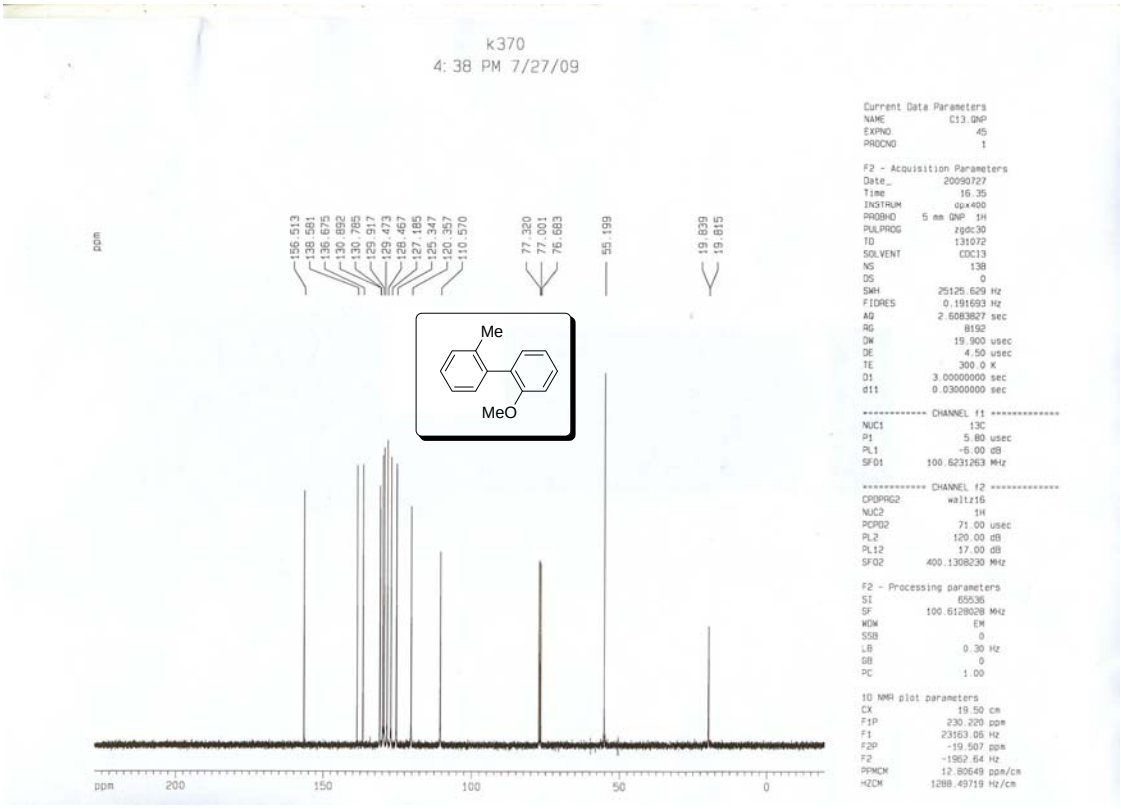
^{13}C NMR of entry 1



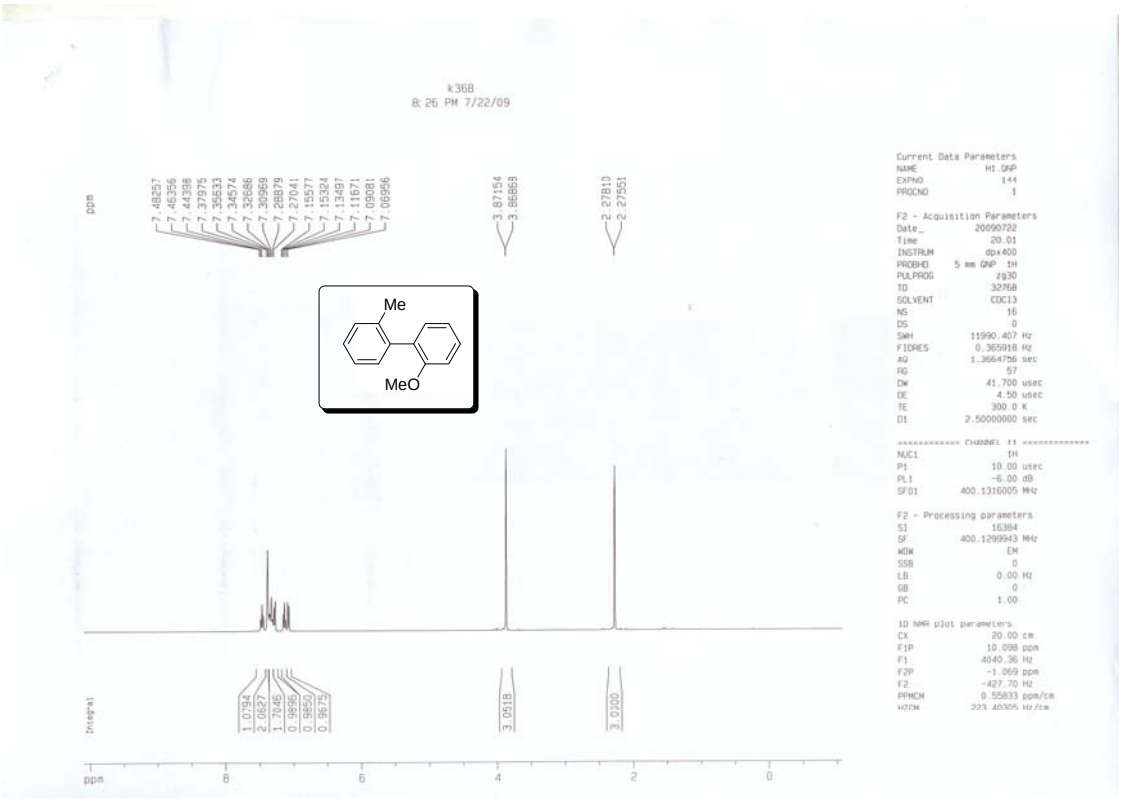
^{1}H NMR of entry 2



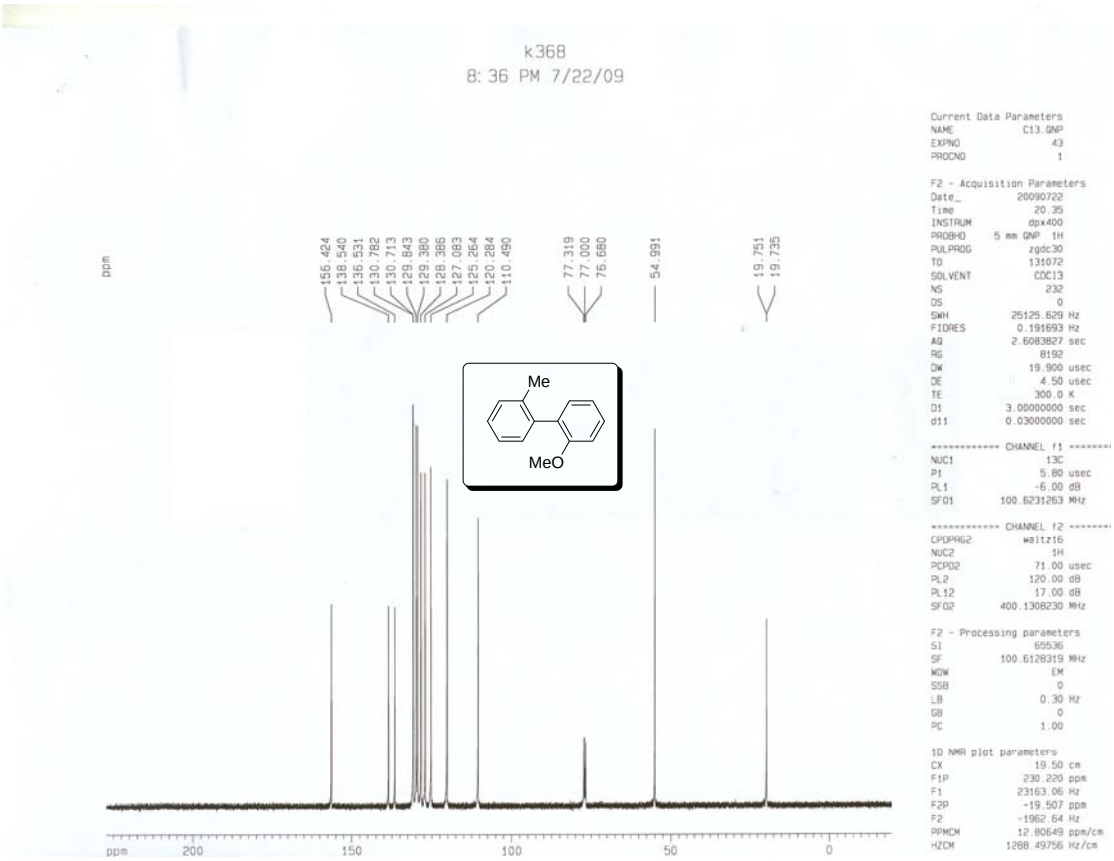
^{13}C NMR of entry 2



^{1}H NMR of entry 3

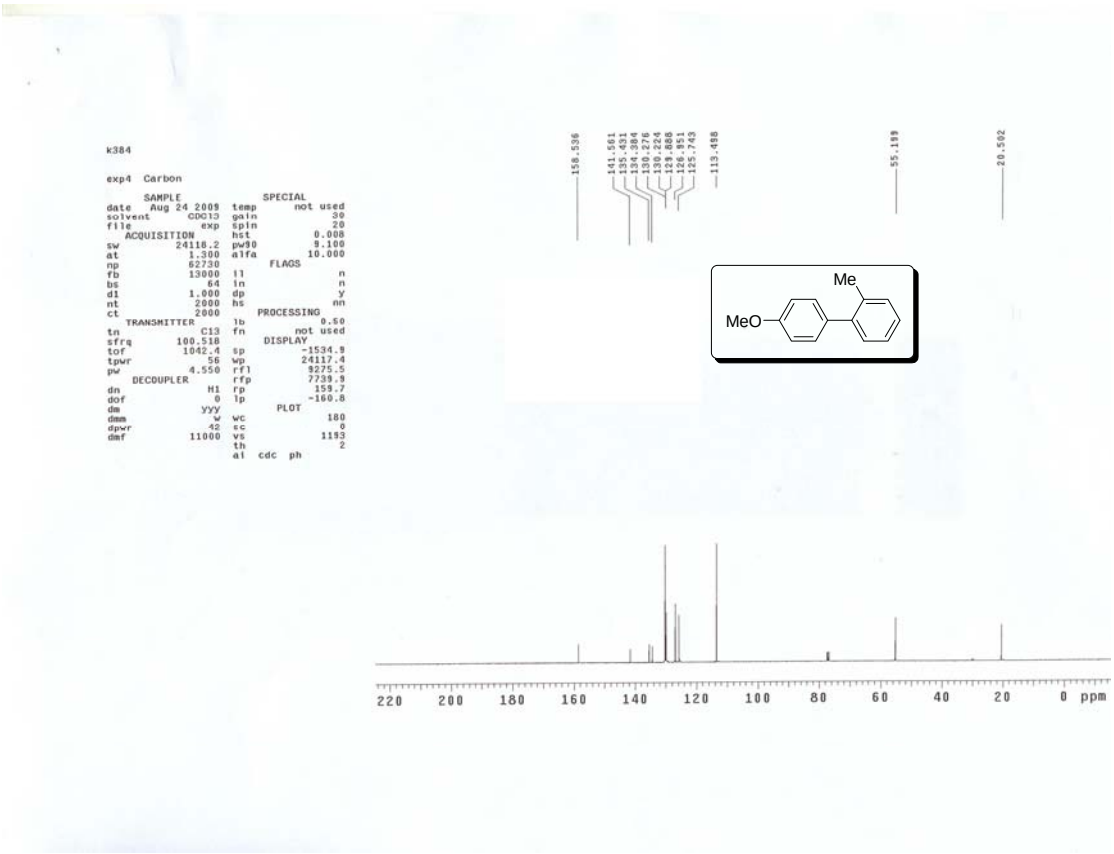


^{13}C NMR of entry 3

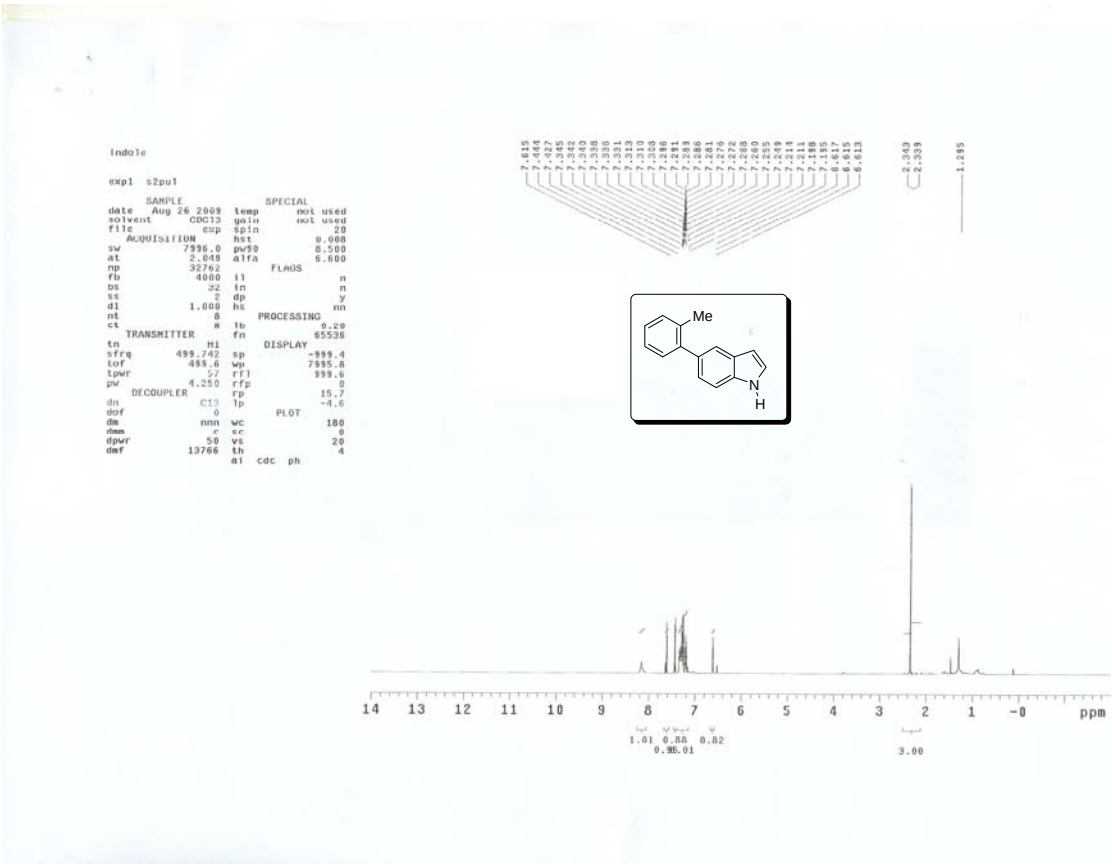


^{1}H NMR of entry 4

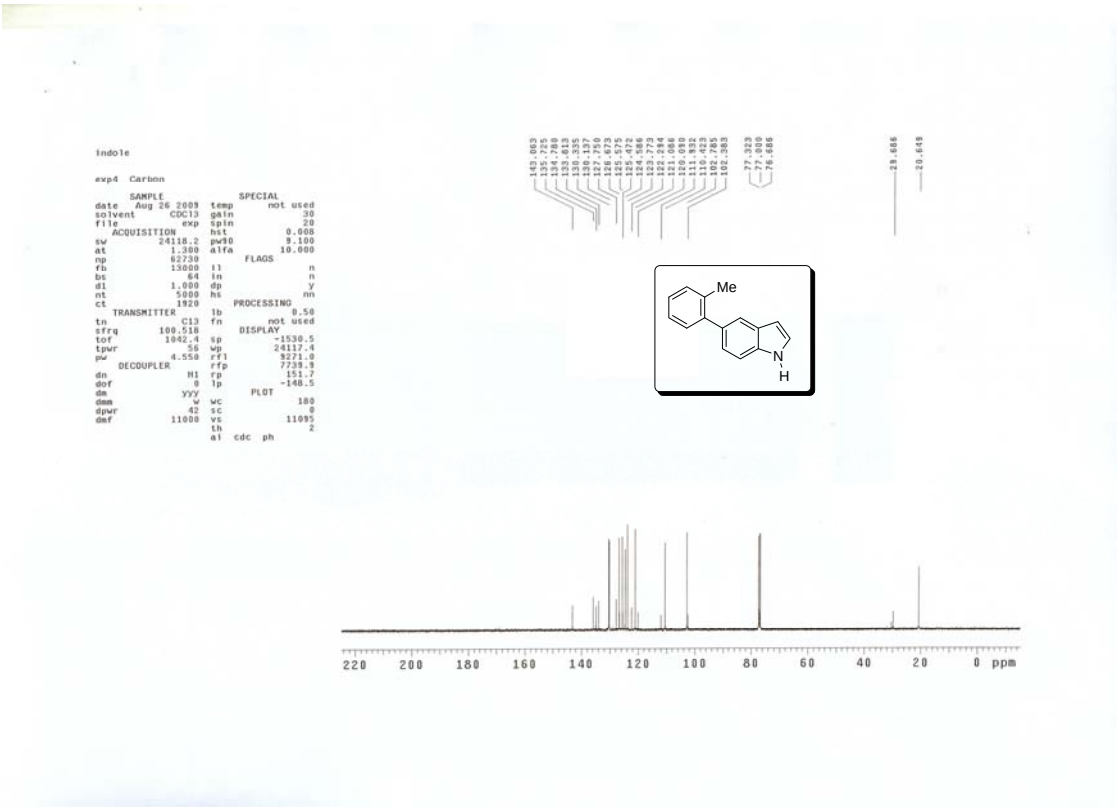
^{13}C NMR of entry 4



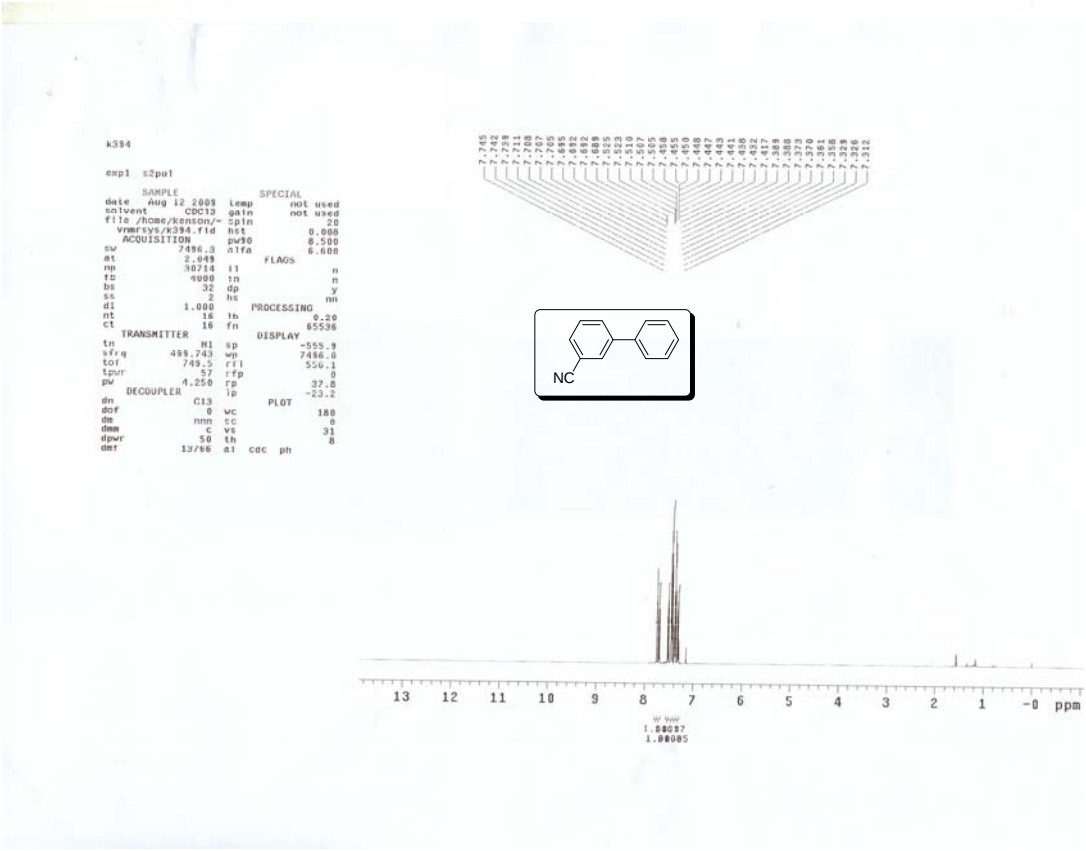
^{1}H NMR of entry 5



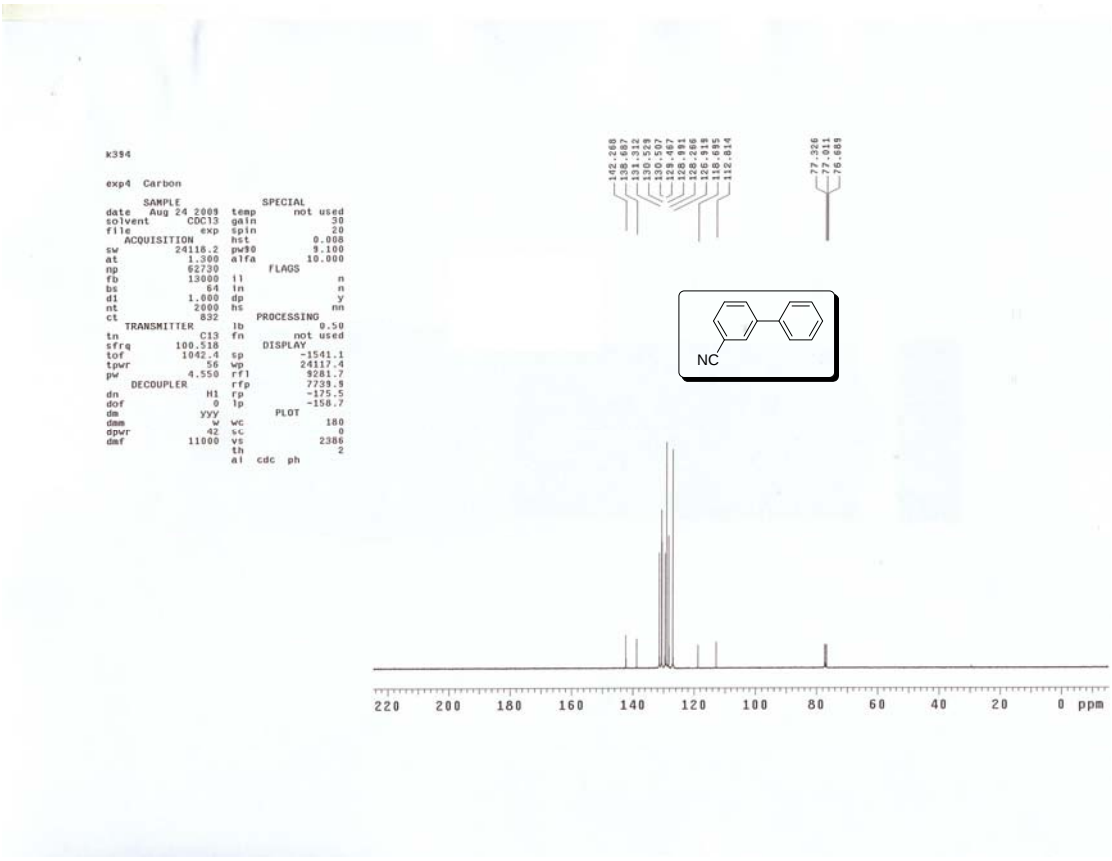
^{13}C NMR of entry 5



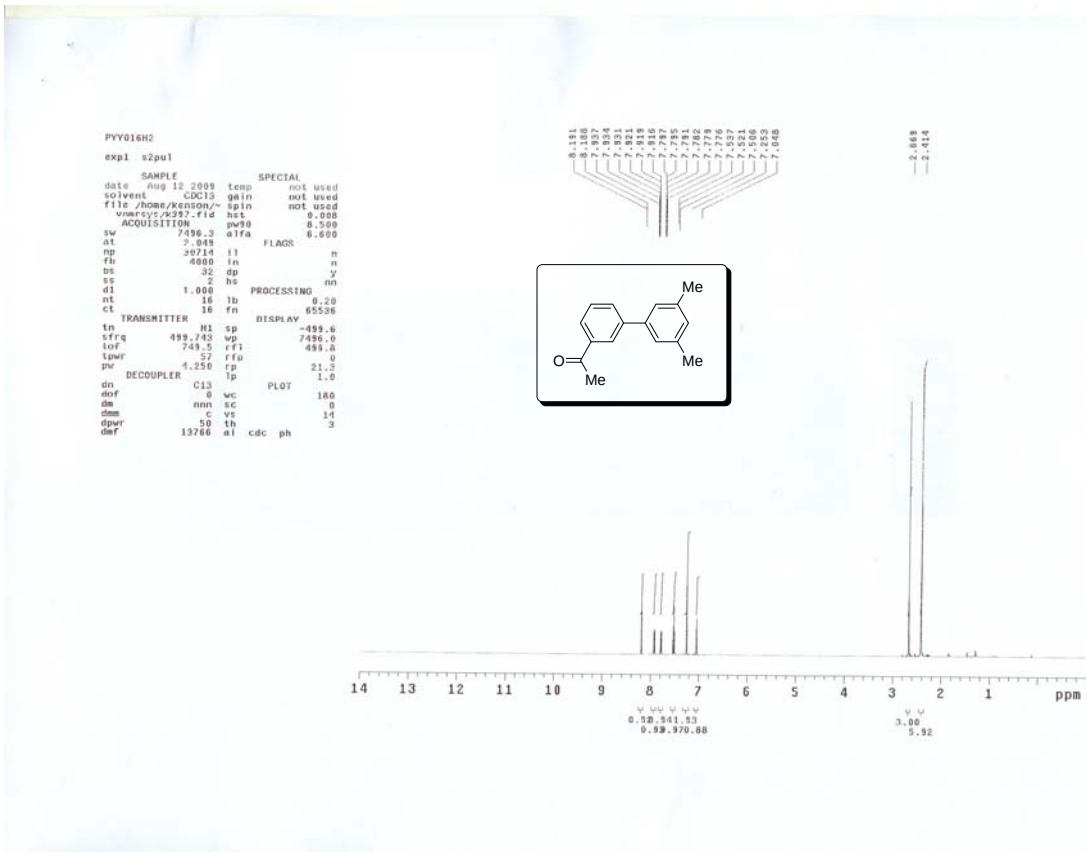
^{1}H NMR of entry 6



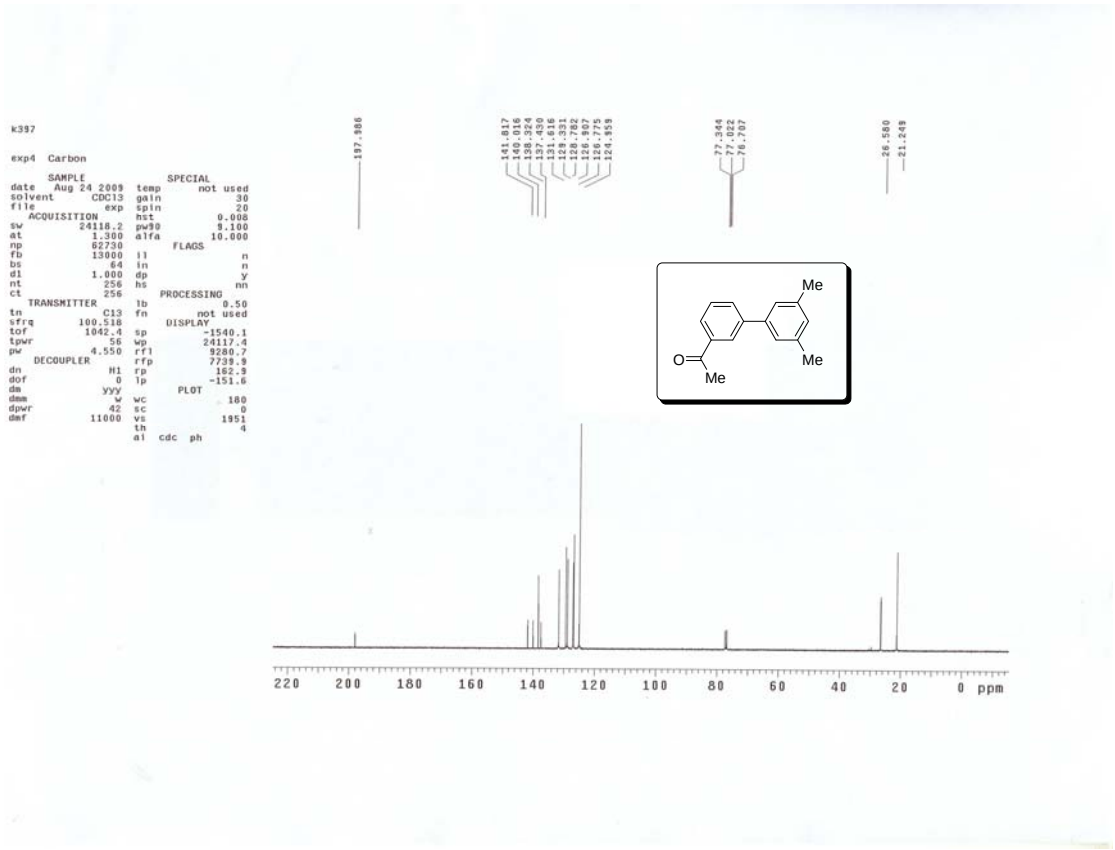
^{13}C NMR of entry 6



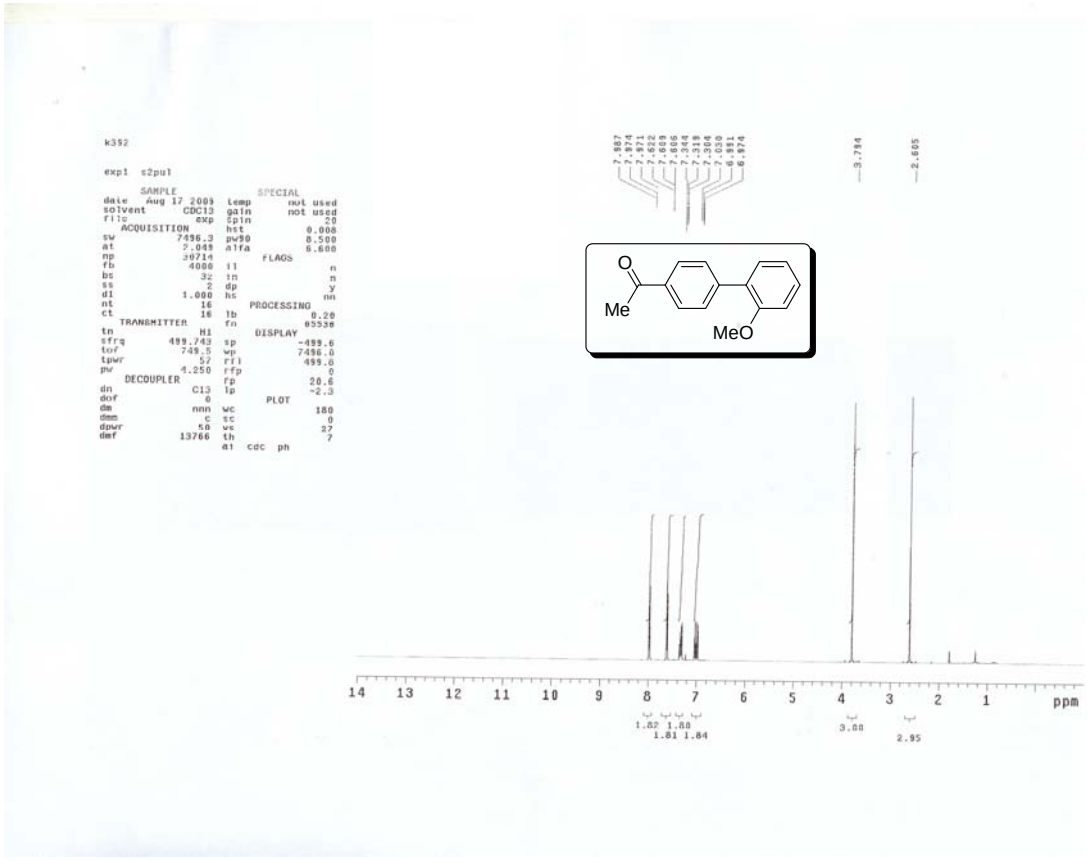
^{1}H NMR of entry 7



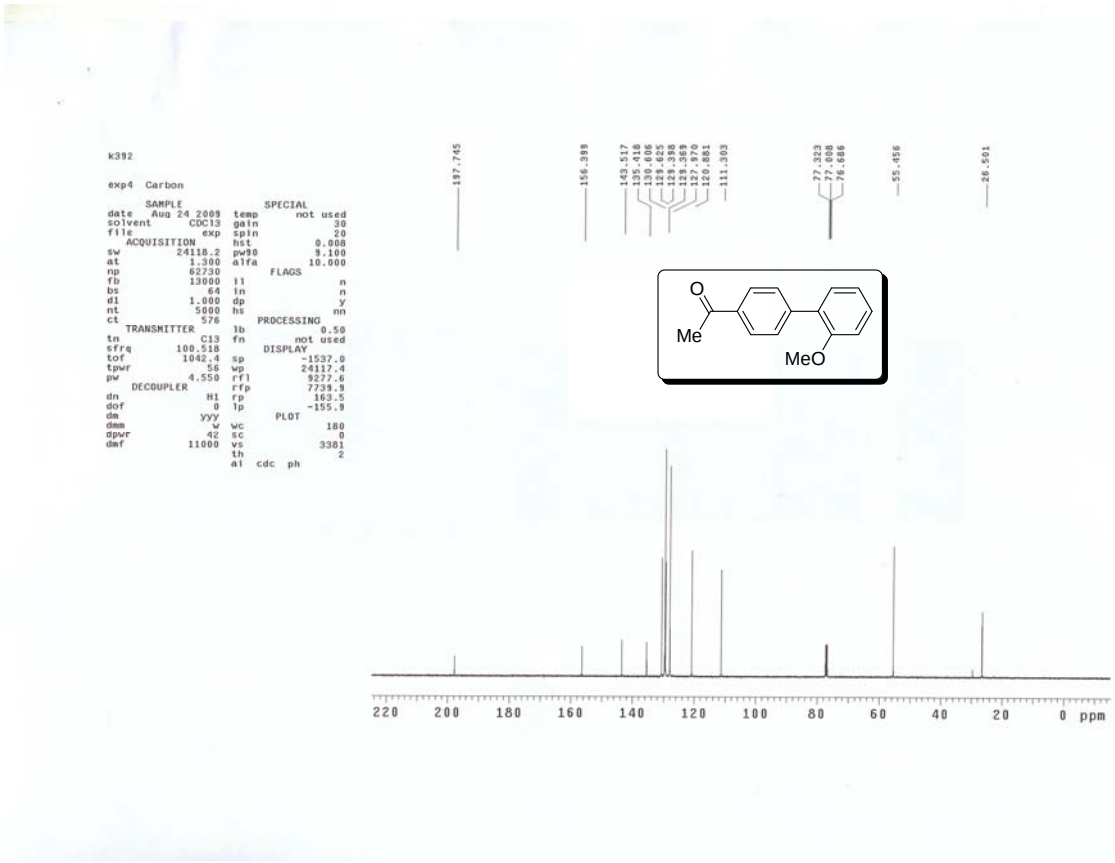
^{13}C NMR of entry 7



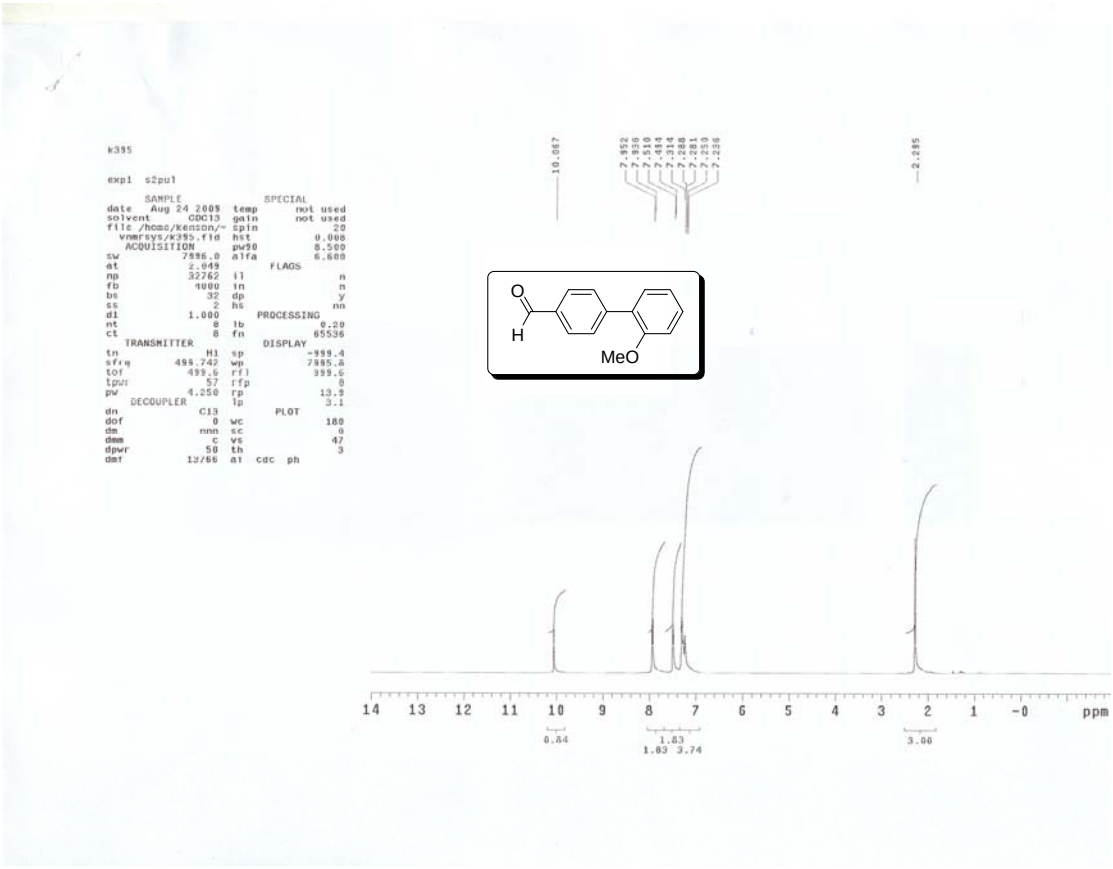
^{1}H NMR of entry 8



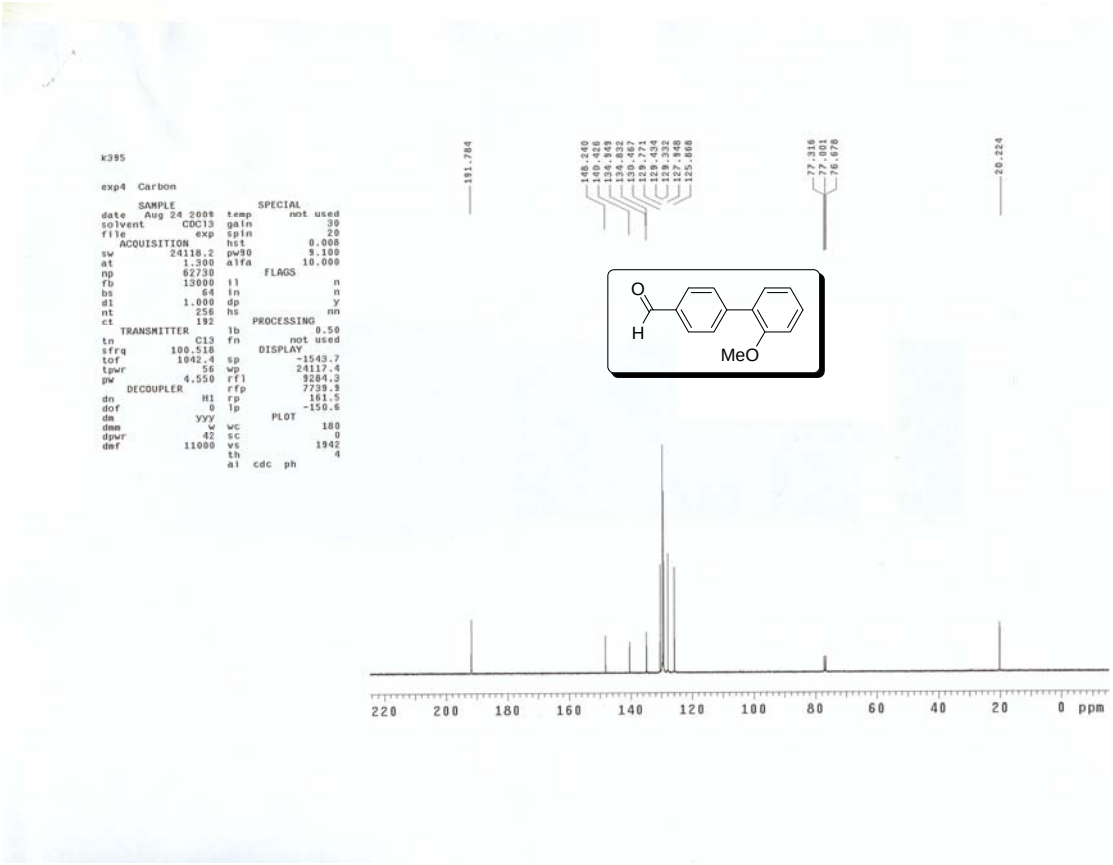
^{13}C NMR of entry 8



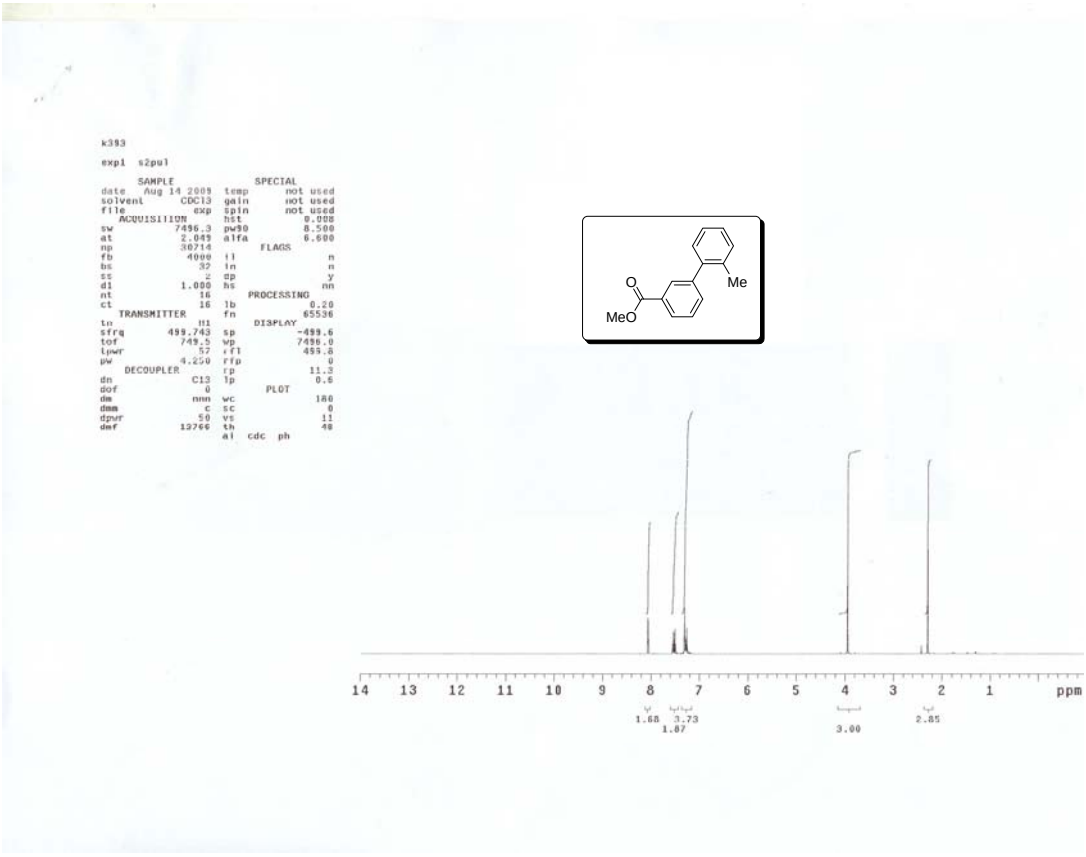
^{1}H NMR of entry 9



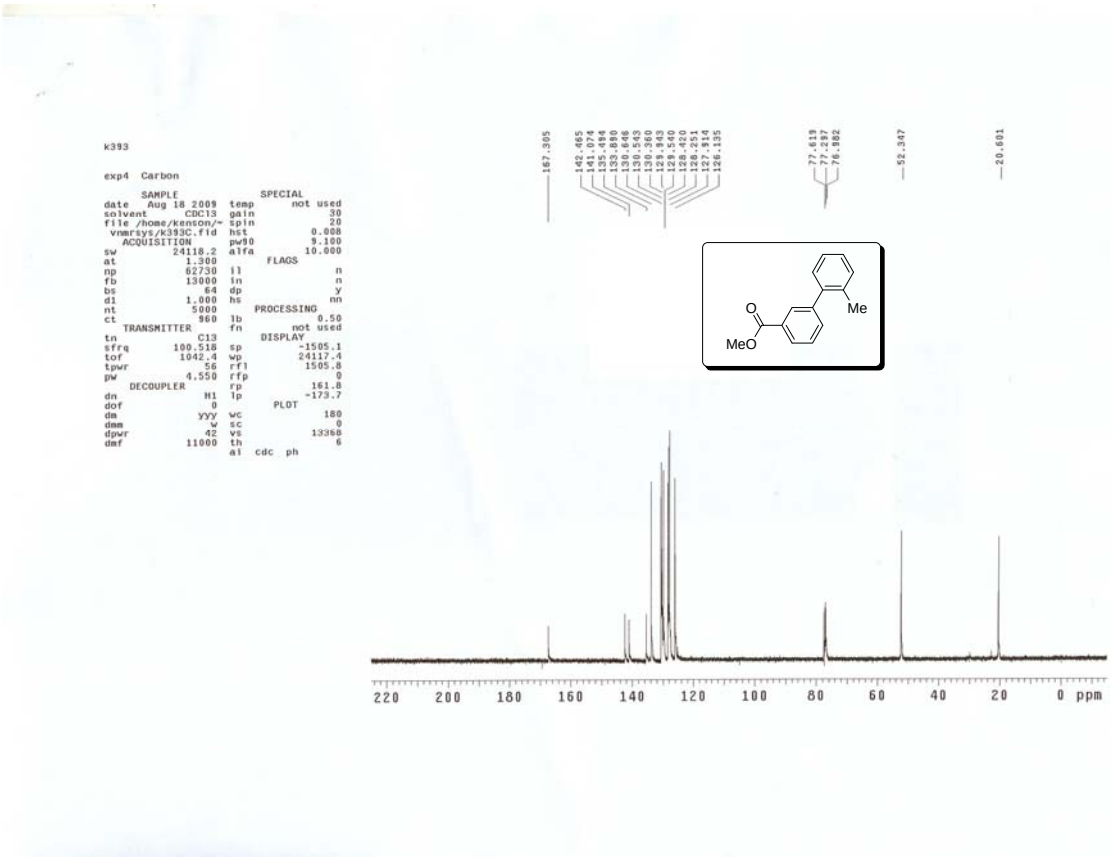
^{13}C NMR of entry 9



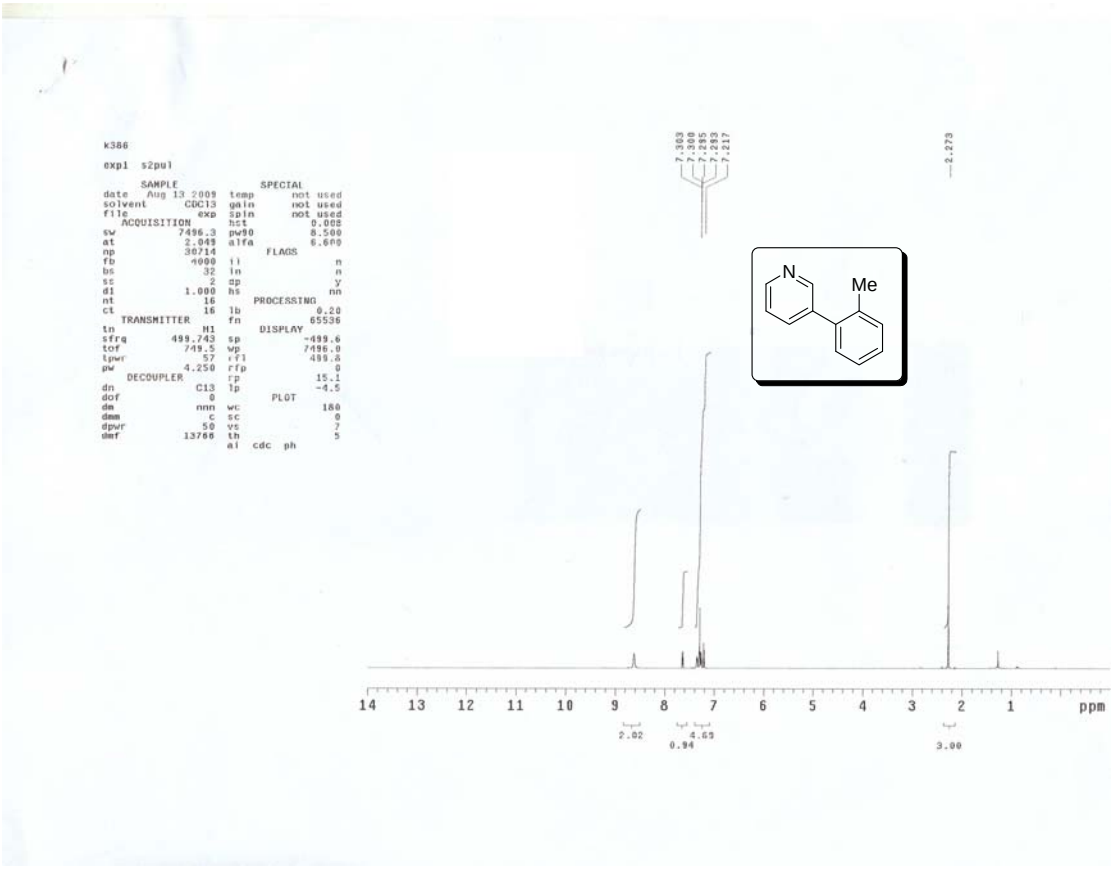
^{1}H NMR of entry 10



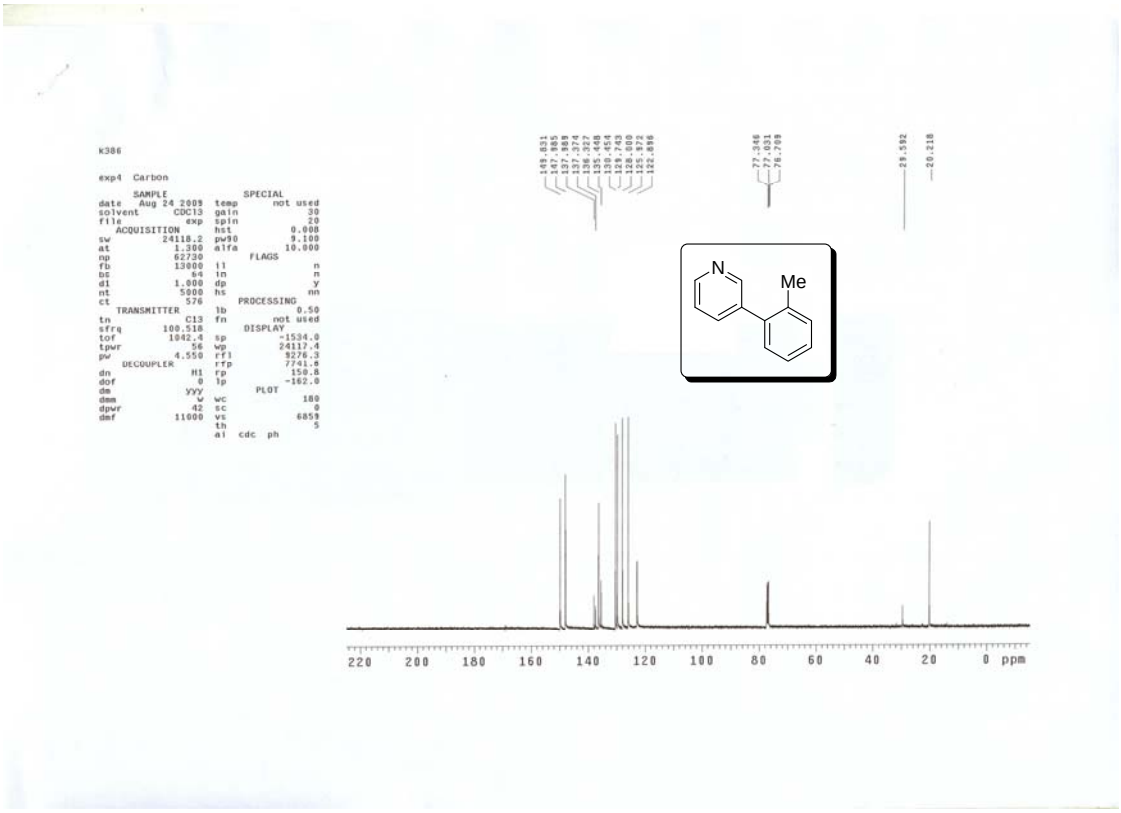
^{13}C NMR of entry 10



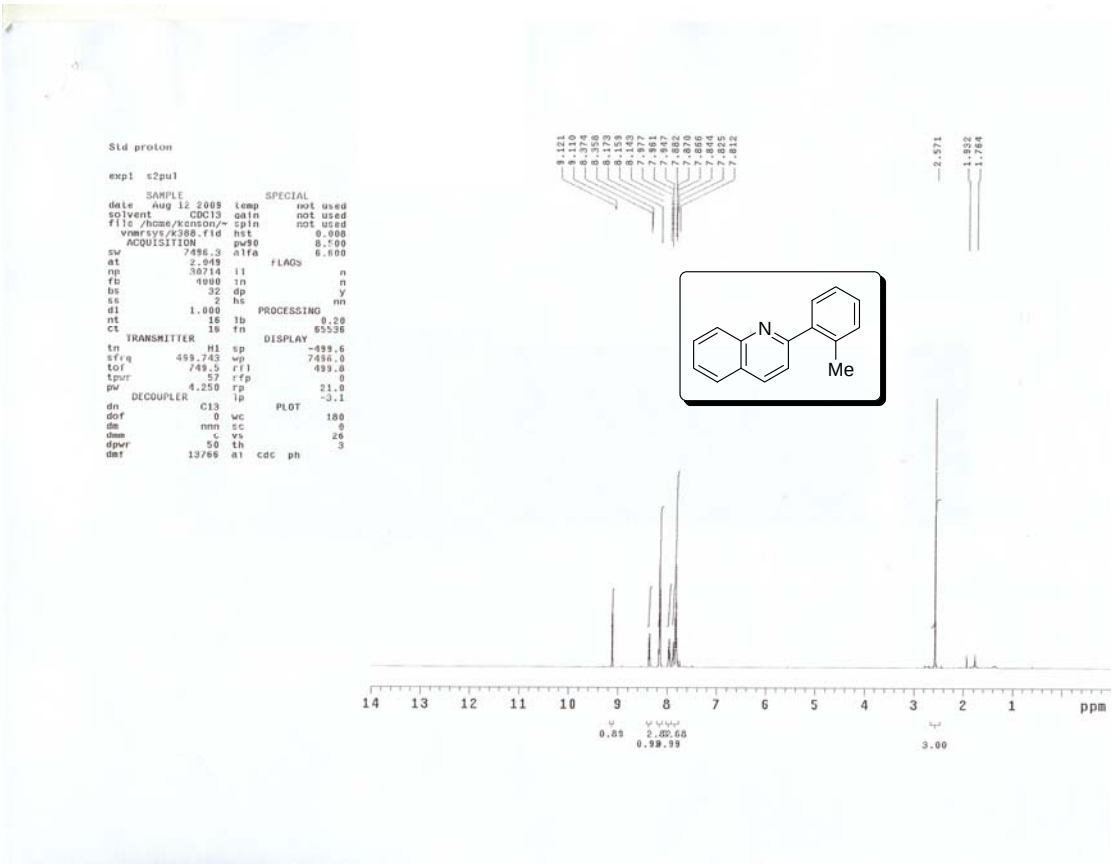
^{1}H NMR of entry 11



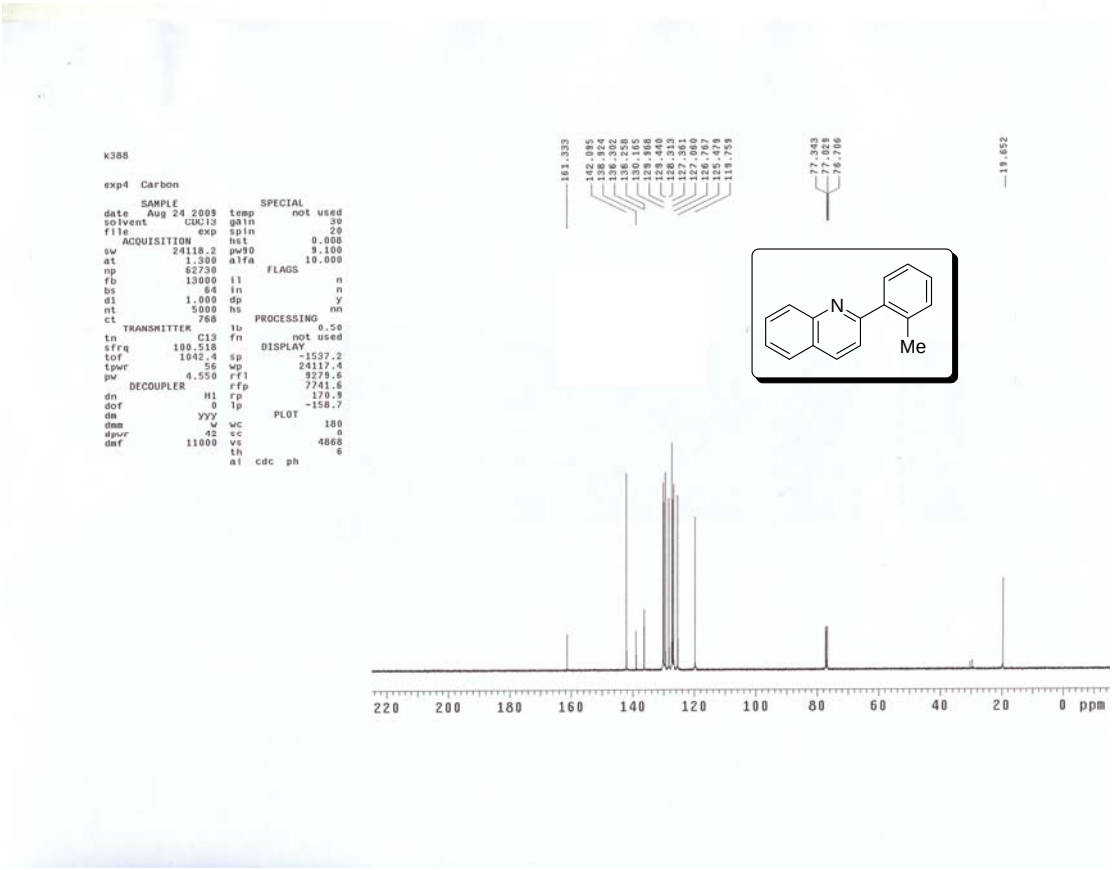
^{13}C NMR of entry 11



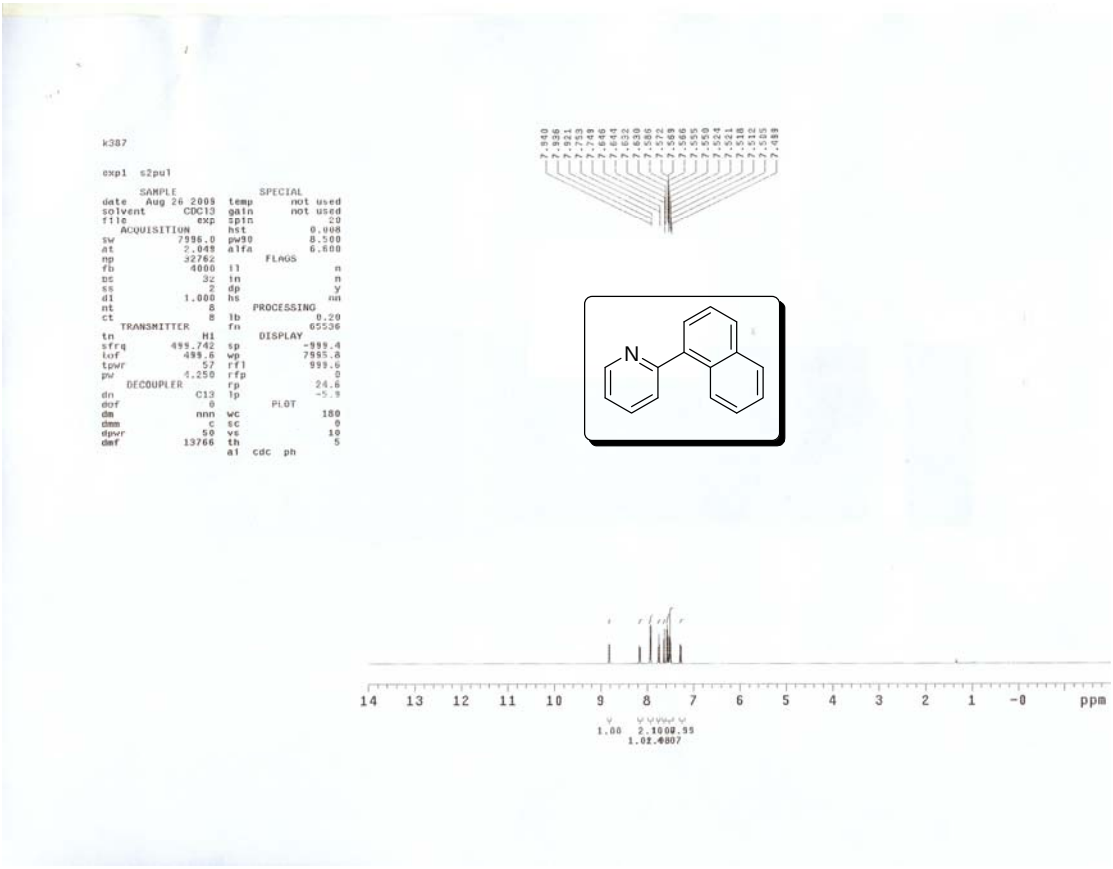
^{1}H NMR of entry 12



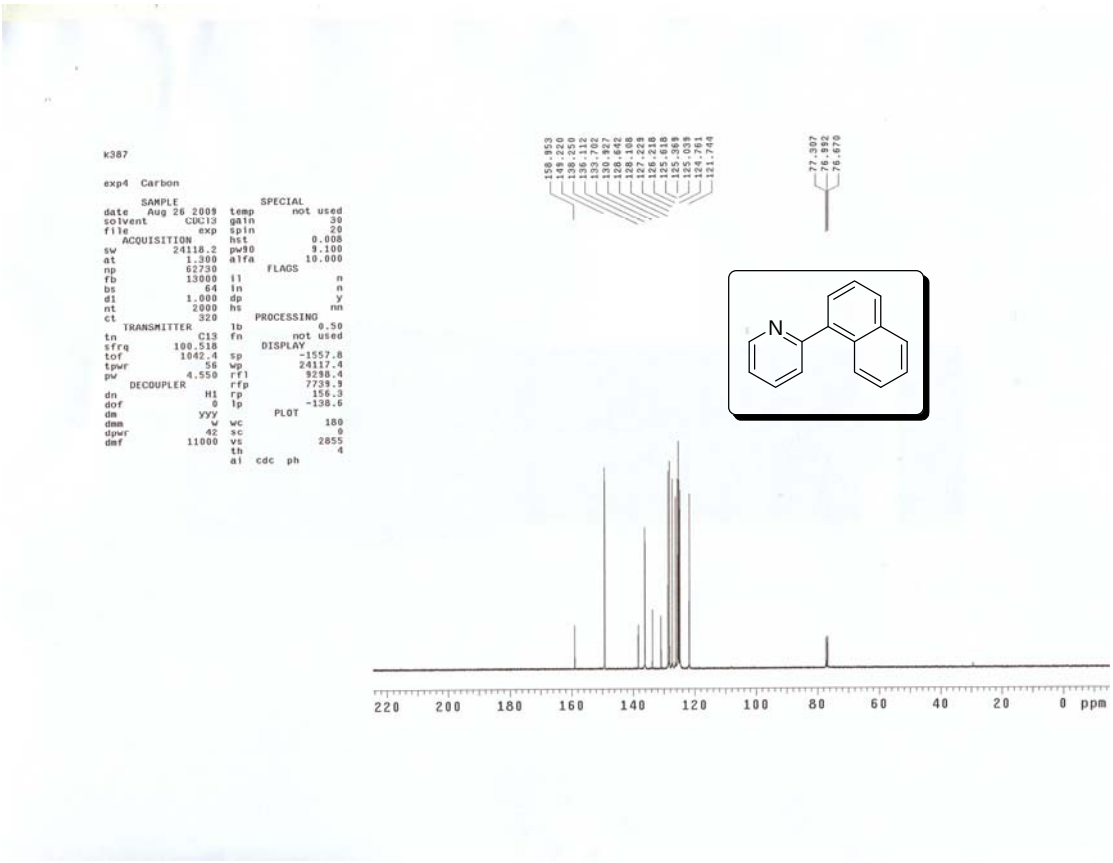
^{13}C NMR of entry 12



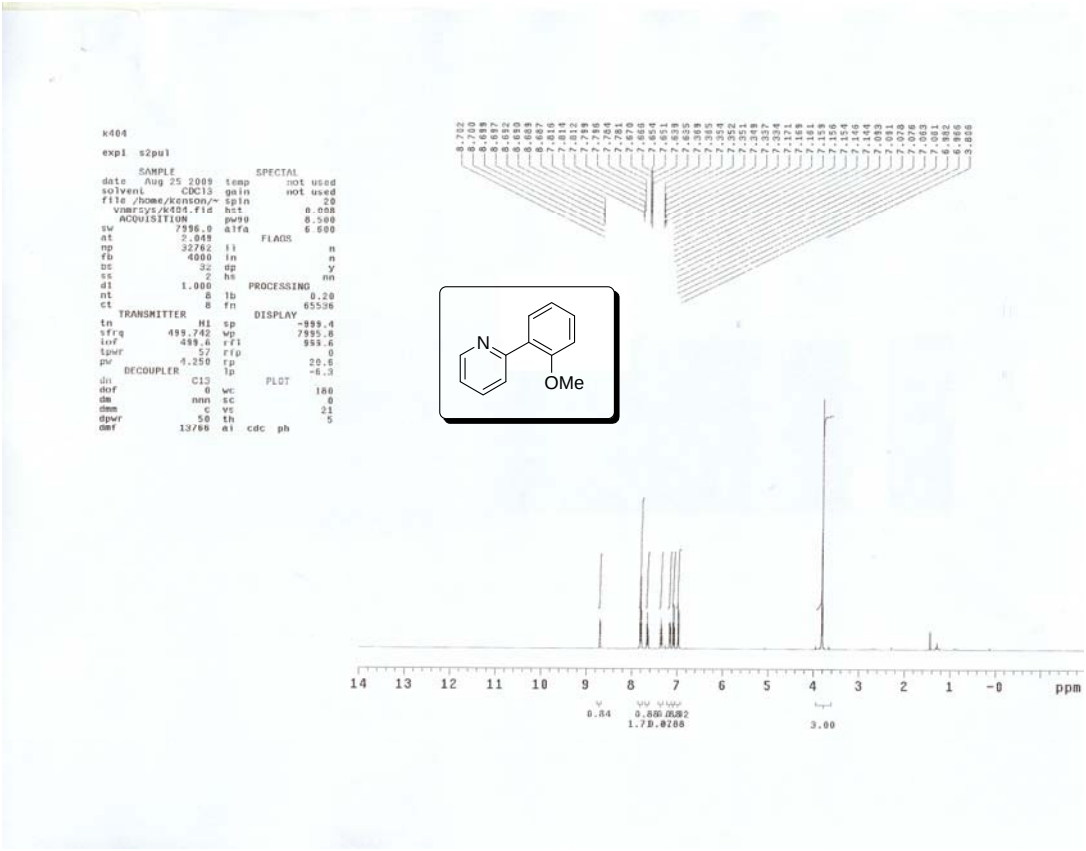
^{1}H NMR of entry 13



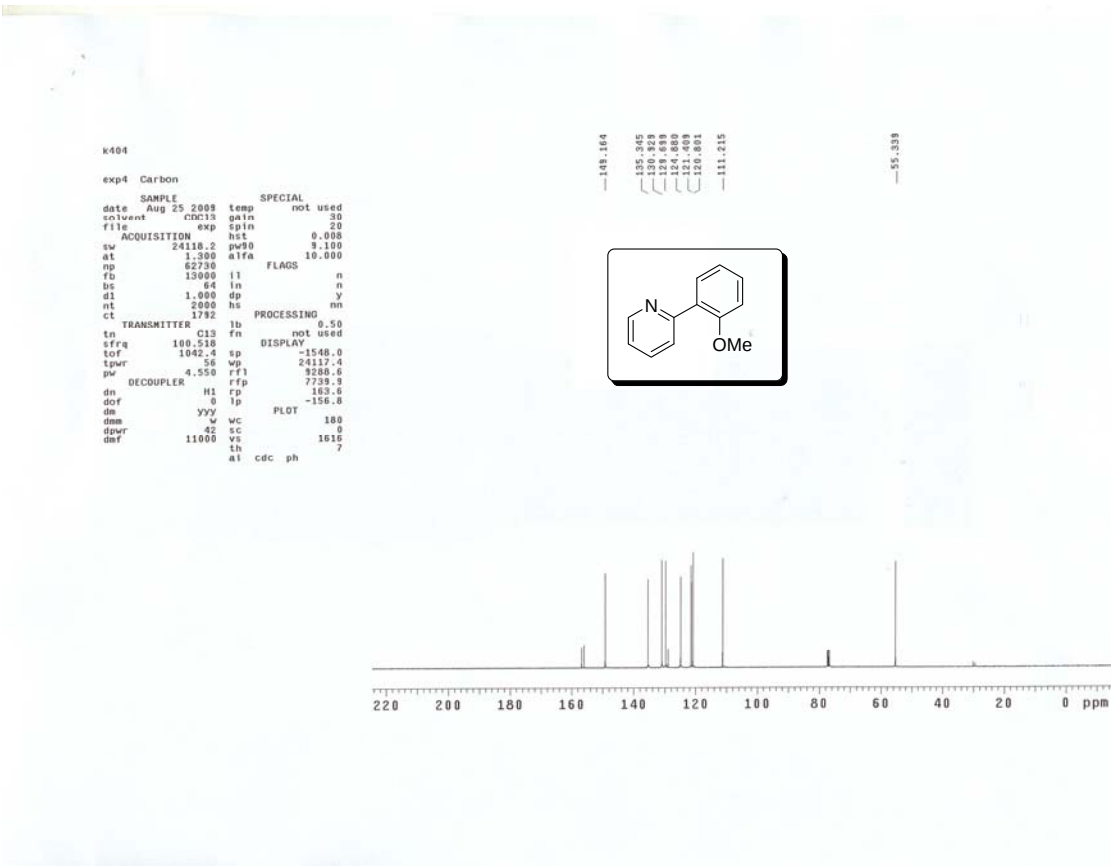
^{13}C NMR of entry 13



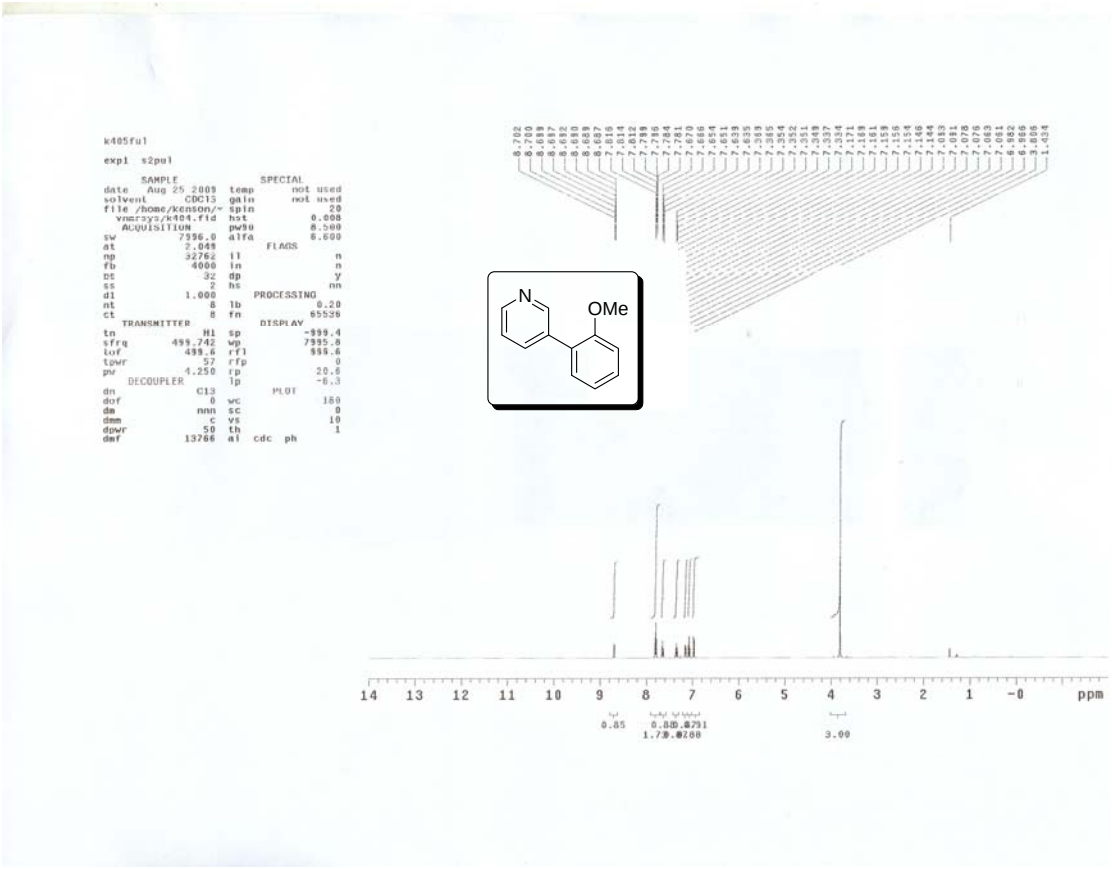
^{1}H NMR of entry 14



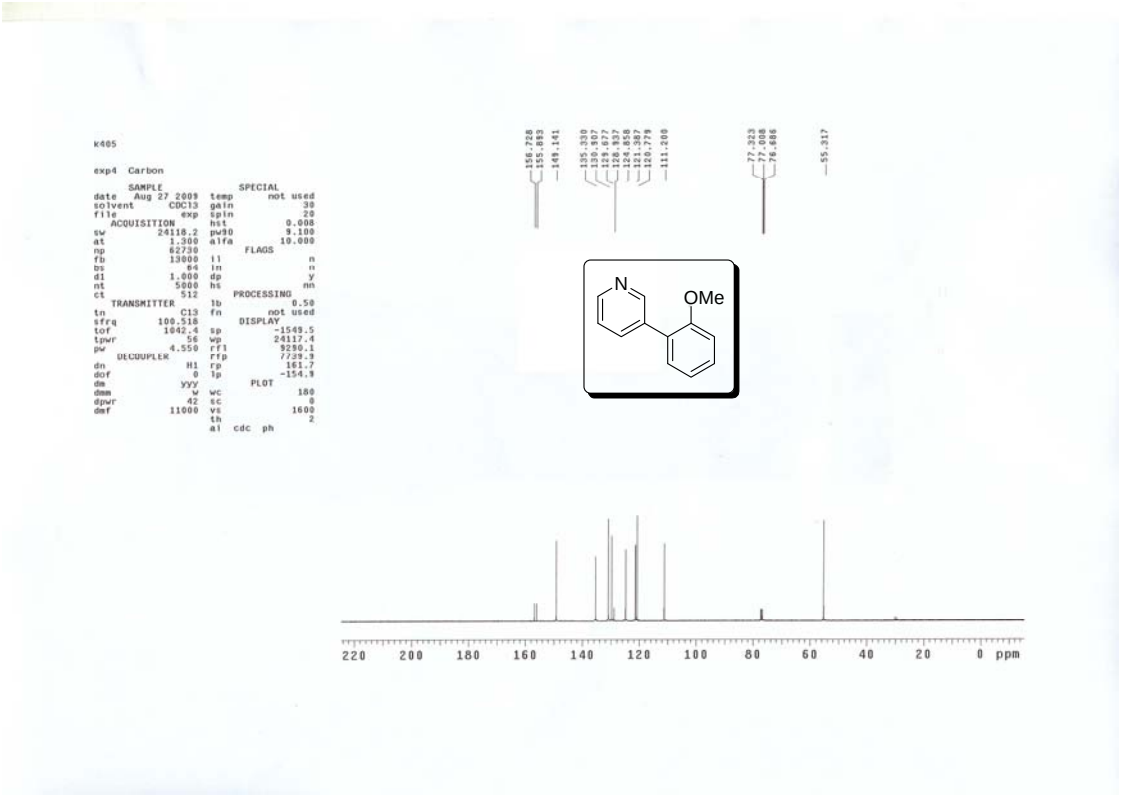
^{13}C NMR of entry 14



^{1}H NMR of entry 15

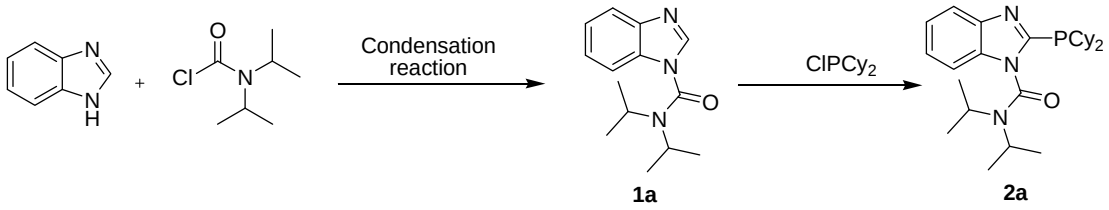


^{13}C NMR of entry 15



Chapter 3: Supporting data of precursors and ligands

Synthesis of N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1a)



General procedures for condensation reaction:

Benzimidazole (2.36g, 20 mmol) was dissolved in 40ml THF in dropping funnel and added dropwisely to the 60ml THF solution contained 1.2 equiv NaH (60% in mineral oil, 0.96g, 24 mmol) at 0℃. NaH was washed with hexane (20 ml × 3) under N_2. The mixture stirred for 1 h at room temperature. After recooling to 0 °C 1.4 equiv N,N-diisopropylcarbamoylchloride (4.58g, 28 mmol) dissolved in 40 ml THF are added to the mixture dropwisely and the mixture is stirred at room temperature over night. Solvent was removed by vacuum. DCM 300 ml and water 100 ml was added to the mixture and the organic phase was separated. The remaining water phase was further extracted with 200 ml DCM twice. The combined organic phase was washed with brine and concentrated. The concentrated mixture was applied to 3 × 3cm silca pad and eluted with dichloromethane. The organic solvent was dried over Na_2SO_4 and evaporated in vacuum. The white powder of N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (4.26g, 87%) was obtained after column chromatography. Melting point: 95.3-96.5℃; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.443 (t, *J* = 6.8Hz, 12H), 3.78-3.85 (m, 2H), 7.28 (s, 1H), 7.35-7.39 (m, 1H), 7.61-7.83 (m, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 8.06 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.9, 49.0, 112.0, 120.3, 123.3, 124.3, 132.5, 140.3, 143.0, 149.4 (Complex unresolved C-P splitting was observed); IR (cm^{-1}) 3081.14, 3004.29, 2971.89, 2932.78, 1690.49, 1481.08, 1445.25, 1377.46, 1344.46, 1301.23, 1213.79, 1136.61, 1064.74, 1027.83, 952.93, 890.93, 829.02, 758.54, 609.88; MS (EI): *m/z* (relative intensity) 245 (M^+, 42), 145 (11), 128 (74), 118 (58), 86 (100); HRMS: calcd. for $C_{14}H_{19}N_3OH^+$: 246.1606, found 246.1610.

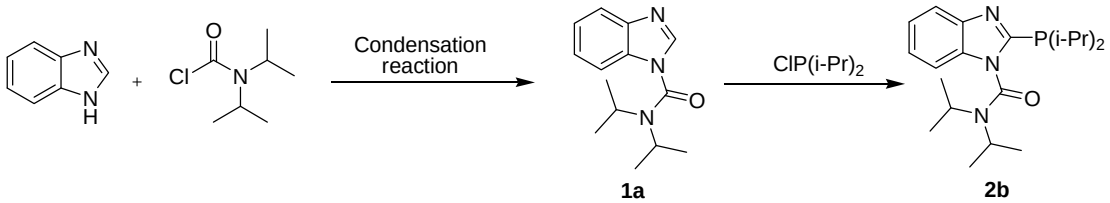
Synthesis of 2-(dicyclohexylphosphino) N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (2a)

General procedures for ligand synthesis:

N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under nitrogen atmosphere. The solution was cooled to -78 °C in dry ice/acetone bath. Titrated n-BuLi (5.5 mmol) was added dropwise by syringe. After the reaction mixture was stirred for an hour at -78°C, chlorodicyclohexylphosphine (1.33 ml, 6.0 mmol) dissolved in 5 ml THF was added dropwise by syringe. The reaction was allowed to warm to room temperature and stirred overnight. Solvent was removed under vacuum. After the solvent was removed under vacuum, the crude product was applied to

column chromatography and the pure product was then dried under vacuum. White solid of title compound (1.61g, 73%) was obtained. Melting point: 205.2-206.8℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-2.70 (m, 34H), 3.39-3.60 (m, 2H), 7.29-7.36 (m, 3 H), 7.89-7.91 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.8, 26.2, 27.0, 30.0, 33.0, 34.9, 110.0, 120.0, 122.7, 123.5, 133.9, 143.7, 150.0, 153.0, 153.3 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -15.95; IR (cm^{-1}) 2926.88, 2848.80, 1693.42, 1437.21, 1371.58, 1329.53, 1300.93, 1255.22, 1201.02, 1147.90, 1028.78, 1002.16, 829.67, 748.43; MS (EI): *m/z* (relative intensity) 440 (M^+, 3), 398 (31), 358 (73), 276 (33), 244 (100), 231 (25), 198 (14), 149 (29); HRMS: calcd. for $C_{26}H_{40}N_3OPH^+$: 442.2987, found 442.3004.

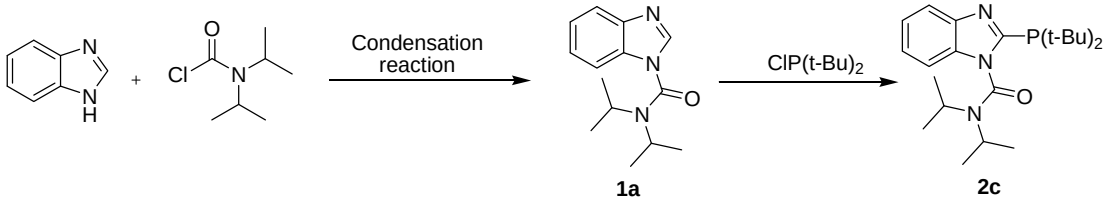
Synthesis of N,N-diisopropyl 2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide (2b)



General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiisopropylphosphine (0.95ml, 6.0 mmol) were used to afford N,N-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide (1.21 g, 67%) as orange solid compound. Melting point: 103.4-104.7℃; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 1.12-1.66 (m, 26H), 2.19-2.79 (m, 2H), 3.48-3.53 (m, 2H), 7.29-7.37 (m, 3H), 7.86-7.89 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 19.7, 20.6, 23.1, 25.1, 110.0, 120.0, 122.7, 123.6, 133.8, 133.9, 143.6, 149.5, 153.2, 153.5 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -7.66; IR (cm^{-1}) 2967.35, 2869.78, 1696.43, 1456.76, 1434.64, 1373.05, 1330.37, 1304.47, 1258.39, 1206.15, 1151.88, 1032.17, 829.88, 746.24; MS (EI): *m/z* (relative intensity) 361 (M^+, 2), 318 (2), 276 (37), 244 (18), 233 (18), 191 (24), 149 (17); HRMS: calcd. for $C_{20}H_{32}N_3OPH^+$: 362.2361, found 362.2365.

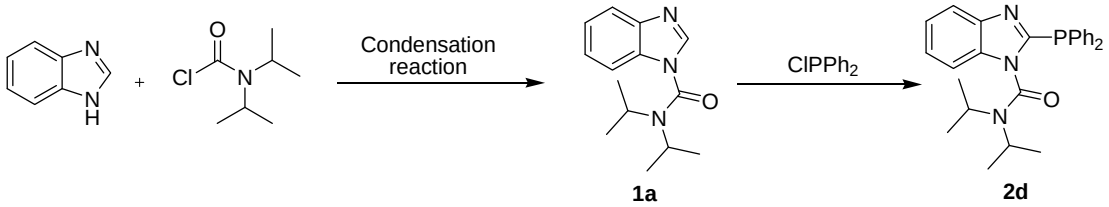
Synthesis of 2-(di-tert-butylphosphino) N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (2c)



General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol), n-BuLi (5.5 mmol), and Di-tertbutylchlorophosphine (1.14 ml, 6.0 mmol) were used to afford 2-(di-tert-butylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.26 g, 65%) as white solid compound. Melting point: 179.2-181.7℃; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11-1.71 (m, 30H), 3.63 (m, 2H), 7.28-7.37 (m, 3H), 7.86-7.89 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.3, 21.4, 30.3, 30.5, 33.7, 46.7, 51.1, 110.2,

120.3, 122.6, 123.6, 132.9, 133.8, 133.8, 143.9, 149.8, 153.0, 153.5 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ 14.35; IR (cm^{-1}) 2966.55, 1698.01, 1467.64, 1436.03, 1369.71, 1320.08, 1257.55, 1200.60, 1072.82, 1029.41, 914.88, 827.80, 748.38, 596.73, 546.15; MS (EI): *m/z* (relative intensity) 388 (M^+, 0), 346 (2), 332 (100), 276 (12), 234 (11), 205 (15), 149 (8); HRMS: calcd. for $C_{22}H_{36}N_3OPH^+$: 390.2674, found 390.2676.

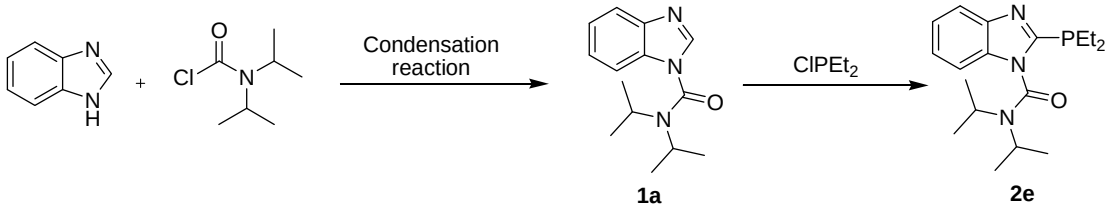
Synthesis of N,N-diisopropyl 2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide (2d)



General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiphenylphosphine (1.33 ml, 6.0 mmol) were used to afford N,N-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide (1.24g, 58%) as white solid compound. Melting point: 182.5-184.3℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.46 (m, 12H), 3.48-3.60 (m, 2H), 7.28-7.39 (m, 9H), 7.60-7.87 (m, 4H), 7.872 (d, *J* = 0.8Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.5, 49.2, 110.1, 120.7, 123.0, 124.1, 128.5, 128.6, 129.3, 133.9, 134.1, 134.2, 144.0, 149.4, 152.7,

152.8 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -25.44; IR (cm^{-1}) 2974.70, 1694.01, 1434.97, 1371.91, 1332.10, 1303.00, 1255.05, 1201.96, 1154.08, 1028.23, 829.83, 747.36, 693.97; MS (EI): *m/z* (relative intensity) 428 (M^+, 1), 386 (14), 344 (57), 301 (25), 244 (100), 223 (20), 201 (29), 183 (45), 159 (16); HRMS: calcd. for $C_{26}H_{28}N_3OPH^+$: 430.2048, found 430.2047.

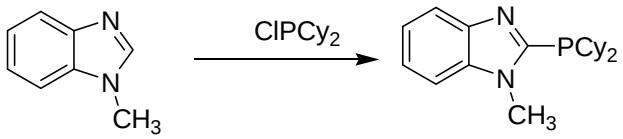
Synthesis of 2-(diethylphosphino) N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (2e)



General procedures for the synthesis of ligand 2a were followed. N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide (1.23 g, 5.0 mmol), n-BuLi (5.5 mmol), and chlorodiethylphosphine (0.73 ml, 6.0 mmol) were used to afford N,N-diisopropyl-2-(diethylphosphino)-1H-benzo[d]imidazole-1-carboxamide (0.86 g, 52%) as white solid compound. Melting point: 89.6-92.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.16 (m, 6H), 1.45 (d, *J* = 6.4 Hz, 12H), 1.88-1.98 (m, 2H), 2.12-2.19 (m, 2H), 3.52 (t, *J* = 5.6 Hz, 2H), 7.29-7.34 (m, 3H), 7.86-7.87 (M, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 9.8, 10.0, 18.4, 20.1, 20.4, 20.6, 109.8, 119.8, 120.9, 122.8, 123.6, 134.2, 143.6, 149.7, 155.1, 155.3 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -28.99; IR (cm^{-1}) 2964.92, 2931.77,

2873.92, 1692.74, 1458.29, 1430.67, 1372.97, 1329.45, 1303.45, 1261.05, 1205.70, 1154.14, 1029.23, 830.66, 744.74; MS (EI): *m/z* (relative intensity) 332 (M^+, 3), 304 (45), 290 (38), 262 (15), 248 (100), 228 (23), 207 (22), 177 (28), 149 (28); HRMS: calcd. for $C_{18}H_{28}N_3OPH^+$: 334.2048, found 334.2043..

Synthesis of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole (2f)

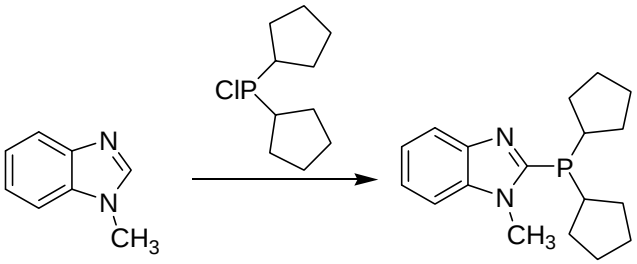


2f

General procedures for the synthesis of ligand 2a were followed. 1-methyl-1H-benzo[d]imidazole (0.66 g, 5.0 mmol) which is commercially available, n-BuLi (5.5 mmol), and chlorodicyclohexylphosphine (1.33 ml, 6.0 mmol) were used to afford 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole (0.98 g, 60%) as white solid compound. Melting point: 113.2-114.7℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21-1.39 (m, 10H), 1.76-1.80 (m, 8H), 1.97-1.99 (m, 2H), 2.32-2.39 (m, 2H), 3.98 (d, *J* = 1.6 Hz, 2H), 7.30-7.41 (m, 3H), 7.87-7.91 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 26.2, 26.6, 26.8, 27.0, 29.2, 29.3, 30.2, 30.3, 31.1, 31.3, 33.4, 33.5, 109.4, 119.8, 121.9, 122.5, 136.3, 144.1, 154.4, 154.6 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -22.55; IR (cm^{-1}) 2921.43, 2847.08, 1443.52, 1406.85, 1318.98, 1270.75, 1235.00, 1002.19, 809.49, 758.68,

724.40; MS (EI): *m/z* (relative intensity) 328 (M^+, 8), 245 (100), 213 (2), 164 (25); HRMS: calcd. for $C_{20}H_{29}N_2PH^+$: 329.2147, found 329.2133.

Synthesis of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole (2g)

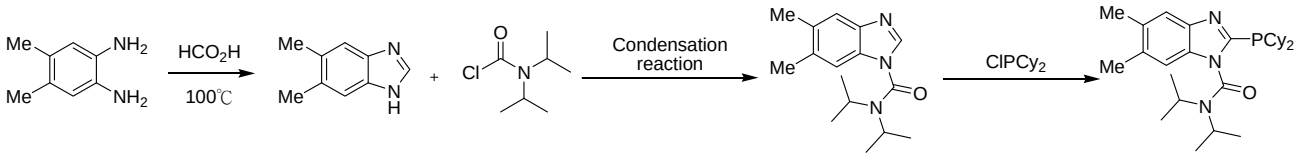


2g

General procedures for the synthesis of ligand 2a were followed. 1-methyl-1H-benzo[d]imidazole (0.66 g, 5.0 mmol) which is commercially available, n-BuLi (5.5 mmol), and chlorodicyclopentylphosphine (1.29 ml, 6.0 mmol) were used to afford 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole (1.17 g, 65%) as white solid compound. Melting point: 74.5-78.4℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.29 (m, 2H), 1.48-1.73 (m, 12H), 2.02-2.06 (m, 2H), 2.63-2.66 (m, 2H), 4.01 (d, *J* = 1.6 Hz, 3H), 7.29-7.32 (m, 2H), 7.38-7.40 (m, 1H), 7.85-7.87 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 25.5, 26.5, 26.6, 31.1, 37.0, 37.1, 110.0, 120.0, 122.0, 122.6, 136.1, 144.1, 156.8, 157.0 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -24.34; IR (cm^{-1}) 2944.91, 2857.45, 1447.26, 1406.21, 1365.01, 1314.55, 1272.97, 1233.63, 1129.77, 1084.77, 904.08,

807.87, 733.84, 681.80, 541.10, 427.17; MS (EI): *m/z* (relative intensity) 300 (M^+, 11), 231 (100), 199 (5), 164 (27); HRMS: calcd. for $C_{18}H_{25}N_2PH^+$: 301.1834, found 301.1826.

Synthesis of 5,6-dimethyl-1H-benzo[d]imidazole (1b)



General procedures for 1b synthesis:

4,5-Dimethyl-1,2-phenylenediamine (2.72, 0.02 mole) which is commercially available was treated with 1.15 ml formic acid (1.5 equiv, 0.03 mole). The mixture was heated under a water bath at 100℃ for two hours. After cooling, sodium hydroxide was added slowly until the mixture was just alkaline to litmus. The crude product was washed with 50ml cold water and 150ml DCM and the organic phase was separated. The remaining water phase was further extracted with 200 ml DCM twice. The combined organic phase was washed with brine and concentrated, following the drying over Na_2SO_4 and evaporated in vacuum. The brown powder (2.75g, 94%) was obtained. Melting point: 184.2-188.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.3 (s, 1H), 6.44 (s, 1H), 7.35 (s, 2H), 7.89 (1H); ^{13}C NMR (100MHz,

$CDCl_3$) δ 18.8, 20.3, 118.6, 127.9, 131.7, 132.2, 139.9 (Complex unresolved C-P splitting was observed); MS (EI): *m/z* (relative intensity) 146 (M^+, 100), 131 (94), 118 (8), 104 (3), 91 (13), 87 (5), 77 (5); HRMS: calcd. for $C_9H_{10}N_2H^+$: 147.0922, found 147.0927.

Synthesis of N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1c)

General procedures for condensation reaction:

5,6-dimethyl-1H-benzo[d]imidazole, **1b**, (2.92g, 20 mmol) was dissolved in 40ml THF in dropping funnel and added dropwisely to the 60ml THF solution contained 1.2 equiv NaH (60% in mineral oil, 0.96g, 24 mmol) at 0℃. NaH was washed with hexane (20 ml × 3) under N_2. The mixture stirred for 1 h at room temperature. After recooling to 0 °C 1.4 equiv N,N-diisopropylcarbamoylchloride (4.58g, 28 mmol) dissolved in 40 ml THF are added to the mixture dropwisely and the mixture is stirred at room temperature over night. Solvent was removed by vacuum. DCM 300 ml and water 100 ml was added to the mixture and the organic phase was separated. The remaining water phase was further extracted with 200 ml DCM twice. The combined organic phase was washed with brine and concentrated. The concentrated mixture was applied to 3 × 3cm silca pad and eluted with dichloromethane. The organic solvent was dried over Na_2SO_4 and evaporated in vacuum. The reddish brown powder of N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (4.10g, 75%)

was obtained after column chromatography. Melting point: 117.1-119.5℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, *J* = 6.8 Hz, 12H), 2.41 (d, *J* = 2.8 Hz, 6H), 3.79-3.86 (m, 2H), 7.41 (s, 1H), 7.58 (s, 1H), 7.95 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.0, 20.3, 20.8, 48.8, 112.2, 120.1, 130.9, 132.1, 133.5, 139.4, 141.5, 149.7 (Complex unresolved C-P splitting was observed); IR (cm^{-1}) 2971.93, 1681.36, 1496.99, 1433.01, 1345.52, 1304.23, 1248.68, 1211.19, 1144.93, 1097.41, 1044.36, 1019.94, 994.95, 909.64, 842.74, 754.86, 646.71, 616.50, 585.00, 554.32, 524.15, 433.79; MS (EI): *m/z* (relative intensity) 273 (M^+, 42), 173 (11), 145 (26), 128 (61), 86 (100); HRMS: calcd. for $C_{16}H_{23}N_3OH^+$: 274.1919, found 274.1922.

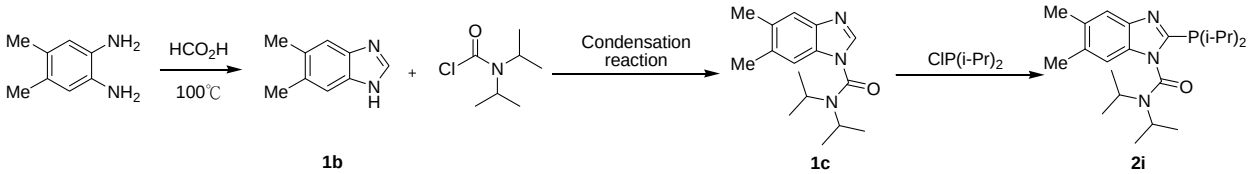
Synthesis of 2-(dicyclohexylphosphino) N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (2h)

General procedures for ligand synthesis:

N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.365g, 5.0 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under nitrogen atmosphere. The solution was cooled to -78 °C in dry ice/acetone bath. Titrated n-BuLi (5.5 mmol) was added dropwise by syringe. After the reaction mixture was stirred for an hour at -78°C, chlorodicyclohexylphosphine (1.33 ml, 6.0 mmol) dissolved in 5 ml THF was added dropwise by syringe. The reaction was allowed to warm to room temperature and stirred overnight. Solvent was removed

under vacuum. After the solvent was removed under vacuum, the crude product was applied to column chromatography and the pure product was then dried under vacuum. White solid of title compound (1.31g, 56%) was obtained. Melting point: 162.5-165.3℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.95 (m, 34H), 2.39 (d, J = 3.6 Hz, 6H), 3.49 (m, 2H), 7.09 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 19.9, 20.2, 20.4, 20.5, 20.6, 46.2, 50.6, 110.4, 120.7, 131.0, 132.2, 133.6, 139.9, 146.8, 149.2, 160.5 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -16.35; IR (cm^{-1}) 2970.33, 1697.80, 1634.45, 1515.61, 1438.33, 1373.10, 1331.74, 1298.93, 1234.28, 1208.02, 1157.10, 1035.95, 810.58, 626.04; MS (EI): *m/z* (relative intensity) 468 (M^+, 9), 426 (27), 386 (64), 343 (9), 304 (18), 272 (100), 259 (23), 177 (55); HRMS: calcd. for $C_{28}H_{44}N_3OPH^+$: 470.3300, found 470.3292.

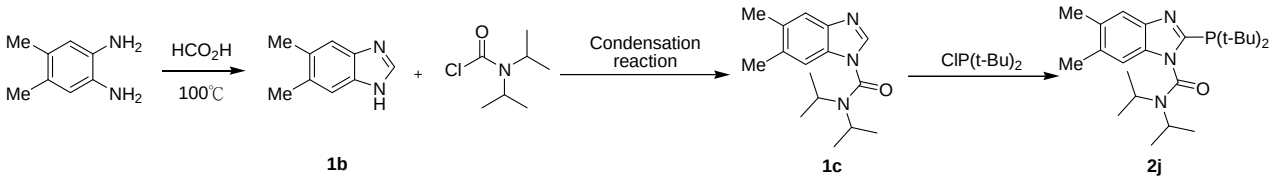
Synthesis of N,N-diisopropyl-2-(diisopropylphosphino) 5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (2i)



General procedures for the synthesis of ligand 2h were followed. N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.365g, 5.0 mmol) which is commercially available, n-BuLi (5.5 mmol), and chlorodiisopropylphosphine (0.95ml, 6.0 mmol) were used to afford

N,N-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-benzo[d]imidazole-1-car boxamide (1.11g, 57%) as orange solid compound. Melting point: 94.8-96.4℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07-1.95 (m, 26H), 2.39 (d, J = 2.0 Hz, 6H), 3.51 (s, 2H), 7.10 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 19.7, 20.2, 20.4, 20.6, 110.1, 119.8, 131.6, 132.5, 132.9, 142.3, 149.8, 152.0, 152.3 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -8.07; IR (cm^{-1}) 2963.39, 2868.49, 1695.01, 1464.11, 1434.71, 1373.01, 1332.31, 1308.69, 1209.16, 1154.84, 1027.41, 1003.84, 878.00, 838.52, 619.02; MS (EI): *m/z* (relative intensity) 389 (M^+, 2), 346 (100), 304 (46), 273 (15), 262 (18), 219 (28), 177 (28), 86 (18); HRMS: calcd. for $C_{22}H_{36}N_3OPH^+$: 390.2674, found 390.2660.

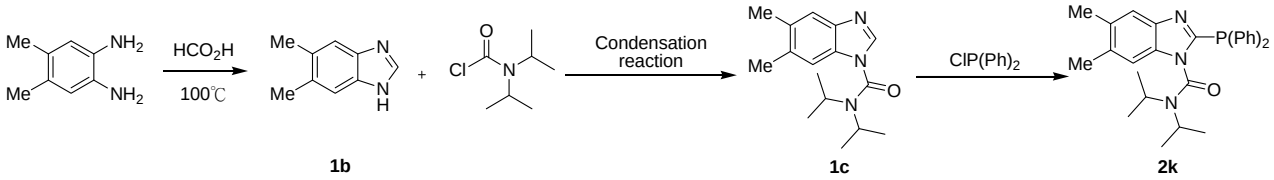
Synthesis of 2-(di-tert-butylphosphino)-N,N-diisopropyl 5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (2j)



General procedures for the synthesis of ligand 2h were followed. N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.365g, 5.0 mmol) which is commercially available, n-BuLi (5.5 mmol), and Di-tertbutylchlorophosphine (1.14 ml, 6.0 mmol) were used to afford 2-(di-tert-butylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-ca rboxamide (1.00g, 48%) as white solid compound. Melting point: 168.4-171.6℃; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 1.14-1.68 (m, 30H), 2.63 (d, *J* = 2.8 Hz, 6H), 3.62-3.65 (m, 2H), 7.10 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.2, 20.5, 30.3, 30.5, 33.7, 110.3, 120.2, 131.5, 132.4, 132.9, 142.6, 150.1, 151.9, 152.2 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ 13.95; IR (cm^{-1}) 2966.65, 1696.82, 1466.79, 1436.62, 1368.95, 1311.06, 1202.72, 1169.01, 1061.29, 1026.91, 910.66, 889.34, 864.47, 837.57, 807.97, 623.78, 591.78, 527.86; MS (EI): *m/z* (relative intensity) 416 (M^+, 0), 374 (3), 360 (100), 318 (5), 304 (10), 262 (15), 233 (28), 177 (20); HRMS: calcd. for $C_{24}H_{40}N_3OPH^+$: 418.2987, found 418.2992.

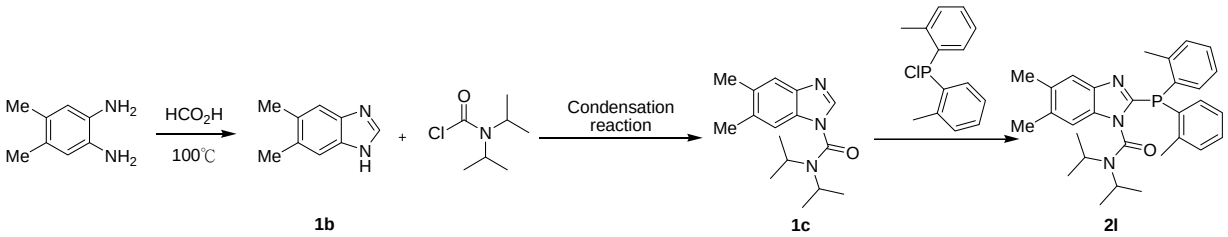
Synthesis of N,N-diisopropyl-5,6-dimethyl-2-(diphenylphosphino) 1H-benzo[d]imidazole-1-carboxamide (2k)



General procedures for the synthesis of ligand 2h were followed. N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (0.546g, 2.0 mmol) which is commercially available, n-BuLi (2.2 mmol), and chlorodiphenylphosphine (0.53 ml, 2.4 mmol) were used to afford N,N-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carbo xamide (0.38g, 42%) as white solid compound. Melting point: 174.6-176.8℃; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28-1.37 (m, 12H), 2.38 (d, *J* = 5.6 Hz, 6H), 3.4-3.61 (m,

2H), 7.11-7.36 (m, 7H), 7.55-8.33 (m, 5H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.2, 20.5, 110.2, 120.6, 128.4, 128.5, 129.1, 132.0, 132.8, 132.9, 133.5, 133.8, 134.0, 134.5, 142.7, 149.7, 151.4, 151.5 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -25.66; IR (cm^{-1}) 3050.16, 2967.16, 2928.78, 1691.23, 1434.42, 1405.18, 1371.81, 1334.72, 1304.95, 1208.83, 1152.97, 1090.58, 1025.99, 883.41, 840.40, 746.11, 692.54, 623.60, 586.65, 507.68, 431.67; MS (EI): *m/z* (relative intensity) 456 (M^+, 1), 414 (15), 372 (45), 346 (9), 329 (27), 272 (100), 256 (22), 201 (25), 183 (49); HRMS: calcd. for $C_{28}H_{32}N_3OPH^+$: 458.2361, found 458.2369.

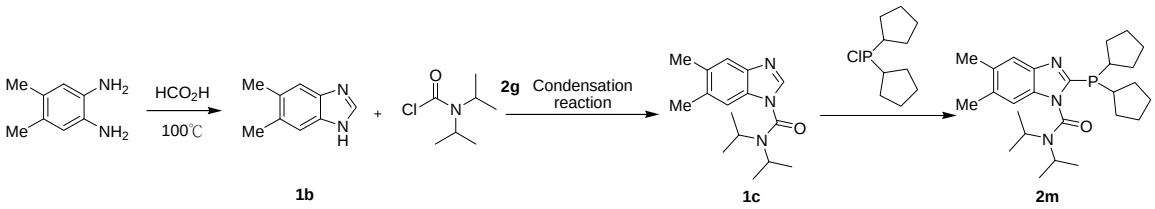
Synthesis of N,N-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino) 1H-benzo[d]imidazole-1-carboxamide (2l)



General procedures for the synthesis of ligand 2h were followed. N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.365g, 5.0 mmol) which is commercially available, n-BuLi (5.5 mmol), and chlorodi(o-tolyl)phosphine (1.492, 6.0 mmol) were used to afford N,N-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-benzo[d]imidazole-1-carbo xamide (1.60g, 77%) as white solid compound. Melting point: 188.2-191.7℃; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 1.22-1.46 (m, 12H), 2.38 (d, *J* = 6.8 Hz, 6H), 2.42 (s, 6H), 3.50-3.58 (m, 2H), 7.11-7.31 (m, 9H), 7,61 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.2, 20.5, 20.6, 21.0, 21.3, 110.2, 120.5, 125.6, 126.3, 128.5, 129.2, 130.0, 131.7, 131.9, 132.0, 133.1, 133.2, 133.3, 133.6, 135.0, 142.2, 142.4, 142.9, 149.6, 150.7, 150.8 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -39.43; IR (cm^{-1}) 3051.33, 2966.69, 1690.59, 14444.41, 1372.89, 1327.06, 1204.19, 1155.99, 1058.60, 835.46, 748.82, 714.18, 586.55, 447.71; MS (EI): *m/z* (relative intensity) 442 (M^+, 9), 400 (18), 357 (19), 272 (100), 229 (18), 207 (73), 187 (19), 165 (13); HRMS: calcd. for $C_{30}H_{36}N_3OPH^+$: 486.2674, found 486.2661..

Synthesis of 2-(dicyclopentylphosphino)-N,N-diisopropyl-5,6-dimethyl -1H-benzo[d]imidazole-1-carboxamide (2m)

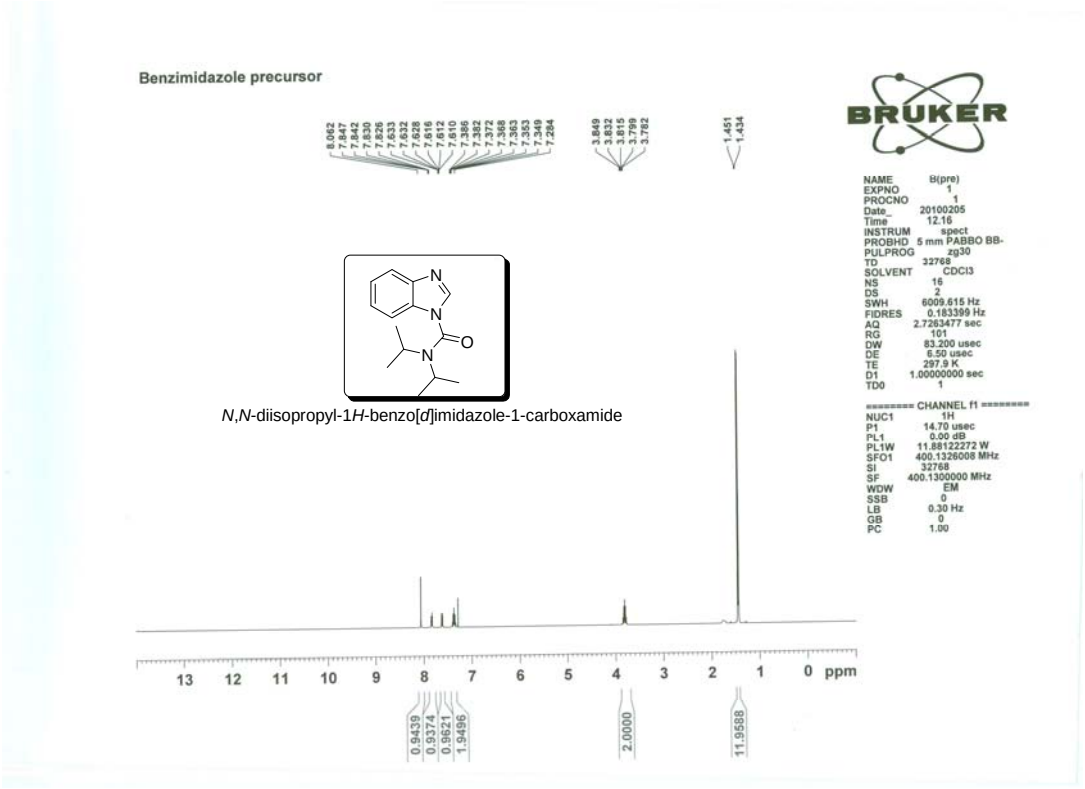


General procedures for the synthesis of ligand 2h were followed. N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.365g, 5.0 mmol) which is commercially available, n-BuLi (5.5 mmol), and chlorodicyclopentylphosphine (1.29 ml, 6.0 mmol) were used to afford 2-(dicyclopentylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide (1.37g, 62%) as white solid compound. Melting point: 171.4-172.8℃; ^1H

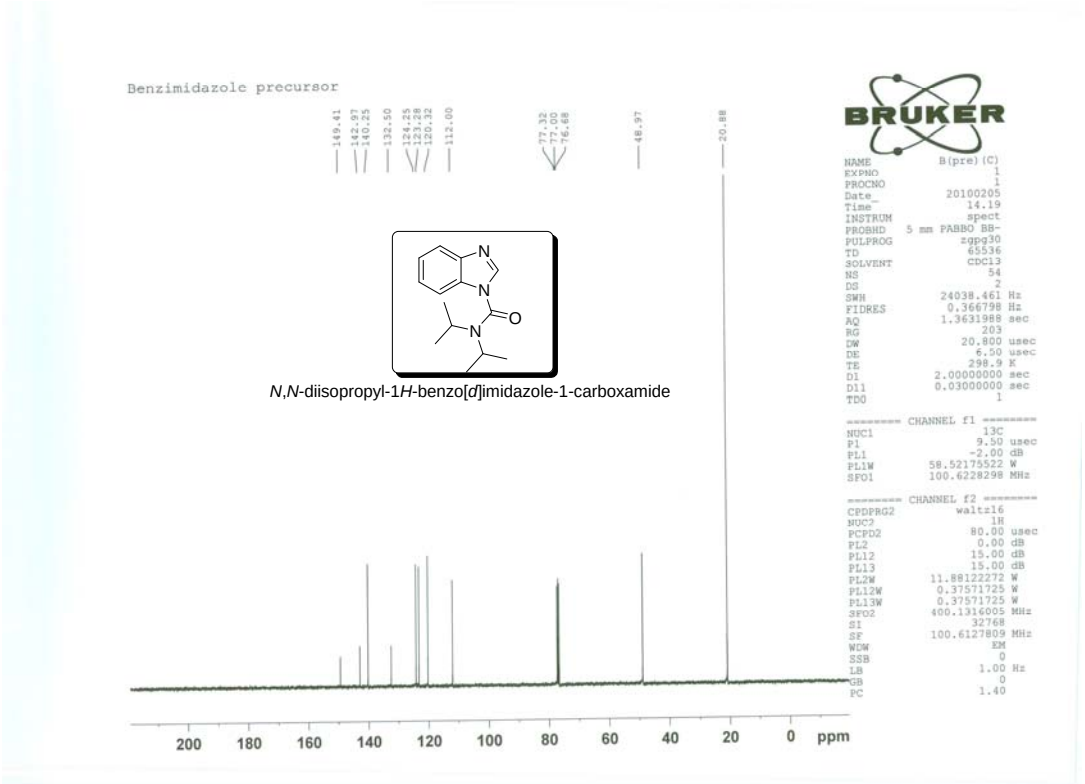
NMR (400 MHz, $CDCl_3$) δ 1.27-2.44 (m, 30H), 2.54 (s, 6H), 3.54 (s, 2H), 7.10 (s, 1H), 7.61 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.2, 20.4, 25.5, 26.3, 30.5, 30.7, 110.1, 119.7, 131.6, 132.2, 132.8, 142.3, 149.7, 154.0, 154.2 (Complex unresolved C-P splitting was observed); ^{31}P NMR (202 MHz, $CDCl_3$) δ -19.70; IR (cm^{-1}) 2952.49, 2864.67, 1696.68, 1436.25, 1372.36, 1331.78, 1305.86, 1211.37, 1157.86, 1060.90, 1027.97, 1003.17, 894.49, 842.03, 625.66, 586.69, 523.09; MS (EI): *m/z* (relative intensity) 440 (M^+, 3), 398 (32), 358 (75), 331 (8), 315 (10), 276 (34), 259 (7), 244 (100), 228 (27); HRMS: calcd. for $C_{26}H_{40}N_3OPH^+$: 442.2987, found 442.2970.

Chapter 3: NMR spectrum and mass spectrum of precursors and ligands

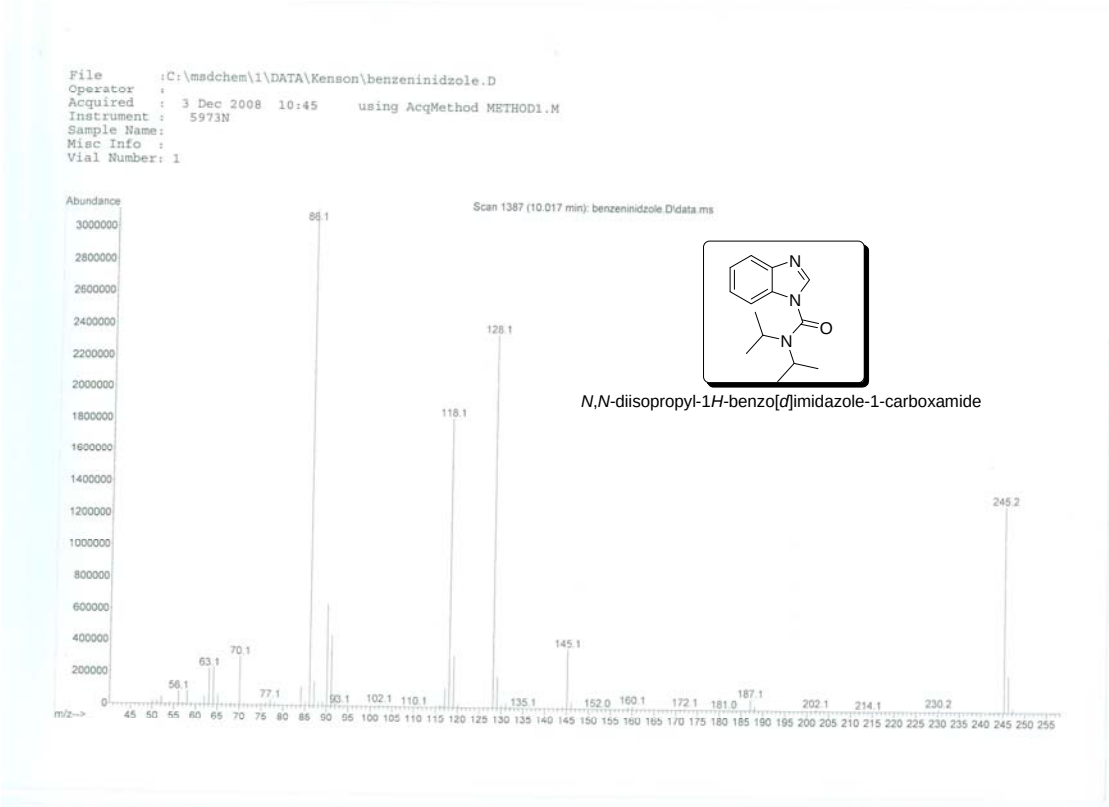
^{1}H NMR of *N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



^{13}C NMR of *N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

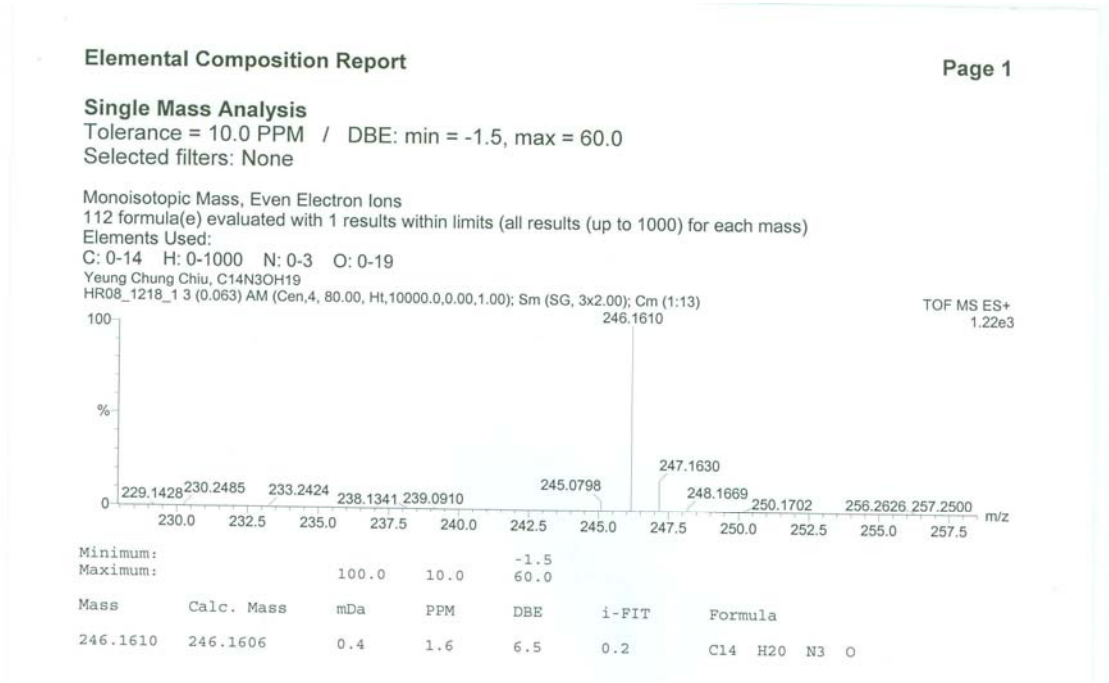


Mass spectrum of *N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

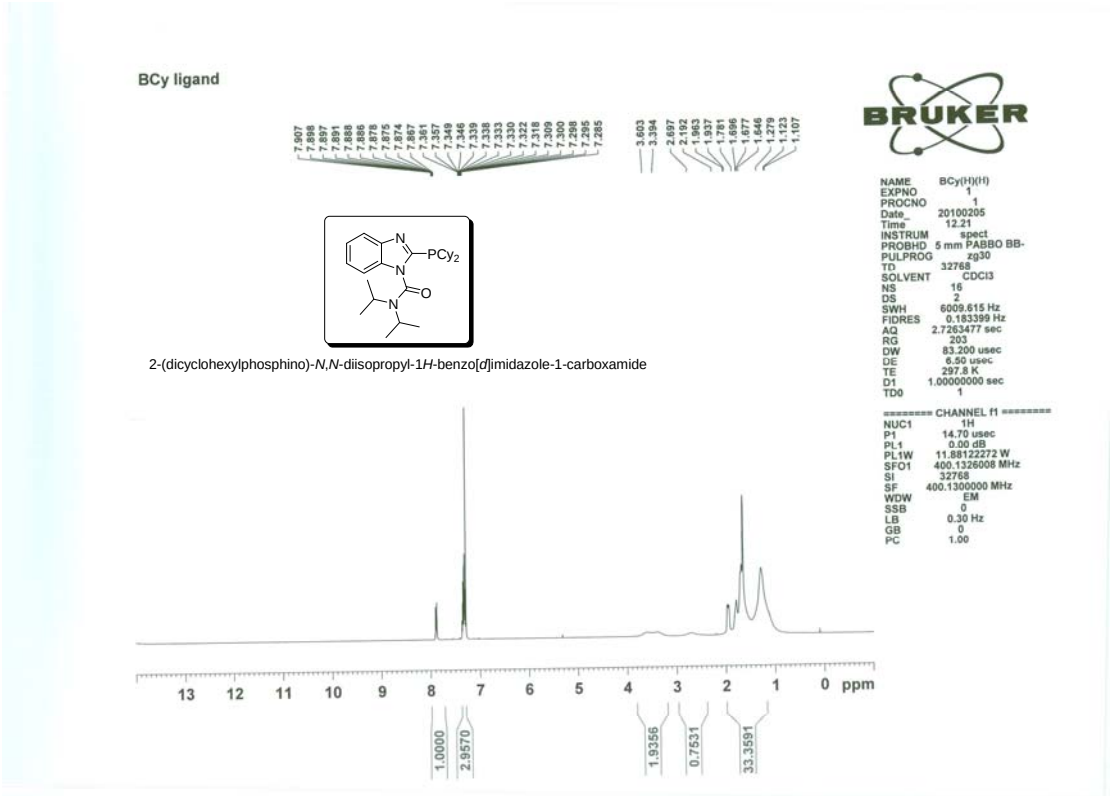


N,*N*-diisopropyl-1*H*-benzo[*d*]imidazole-1-carboxamide

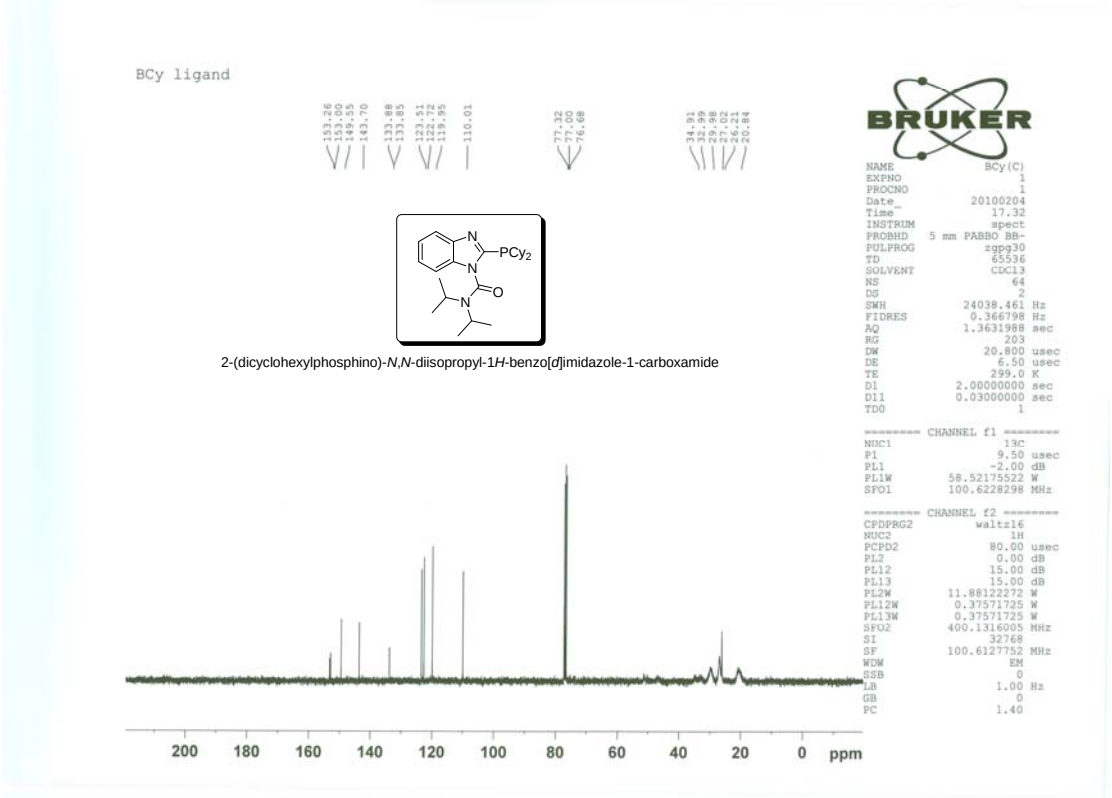
High resolution mass spectrum of *N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



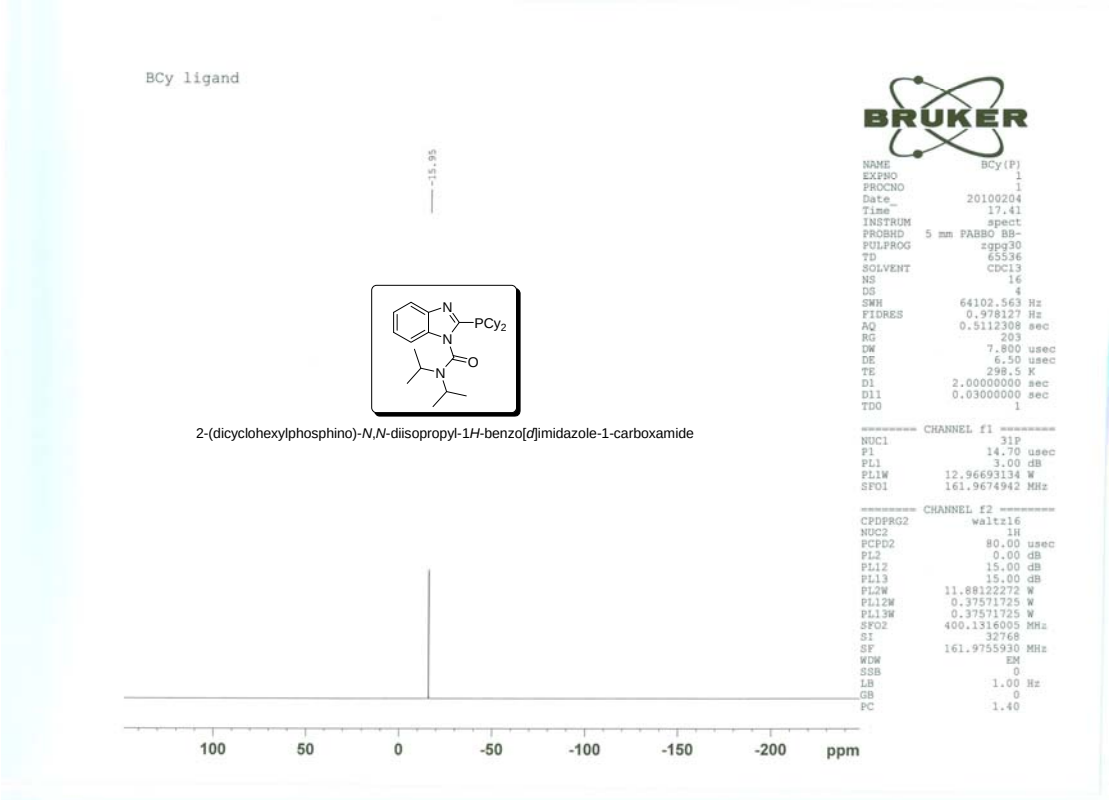
^{1}H NMR of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



^{13}C NMR of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

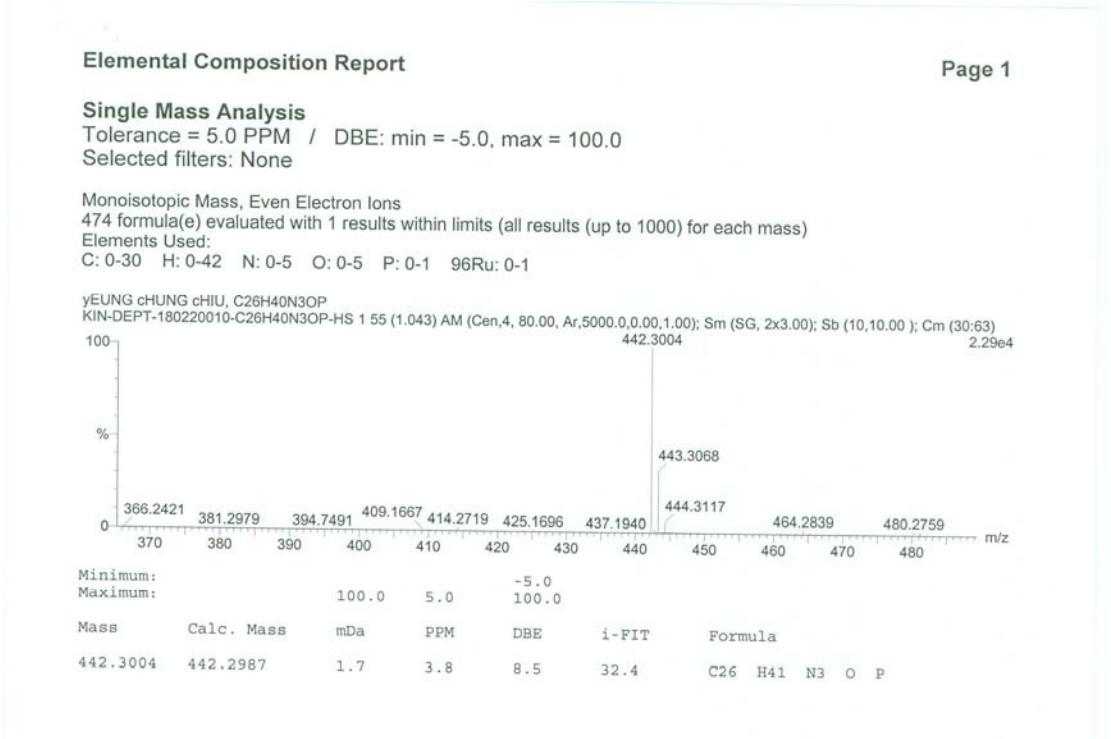


^{31}P NMR of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

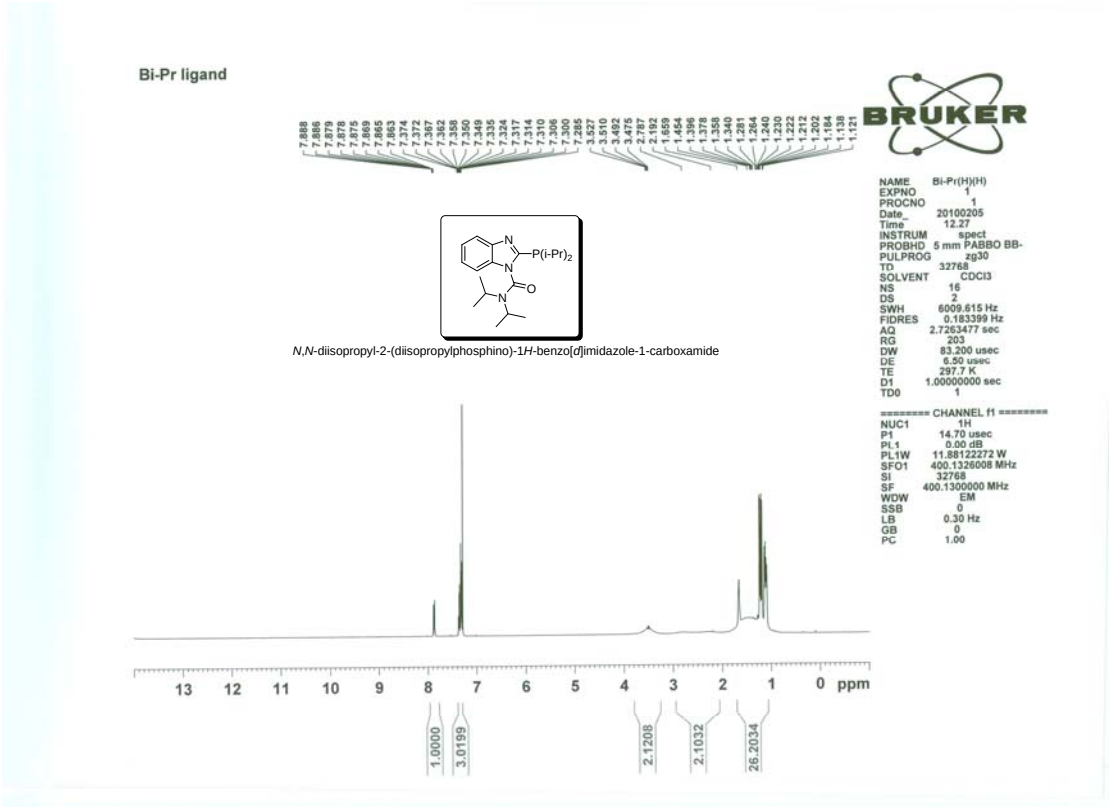


High resolution mass spectrum of

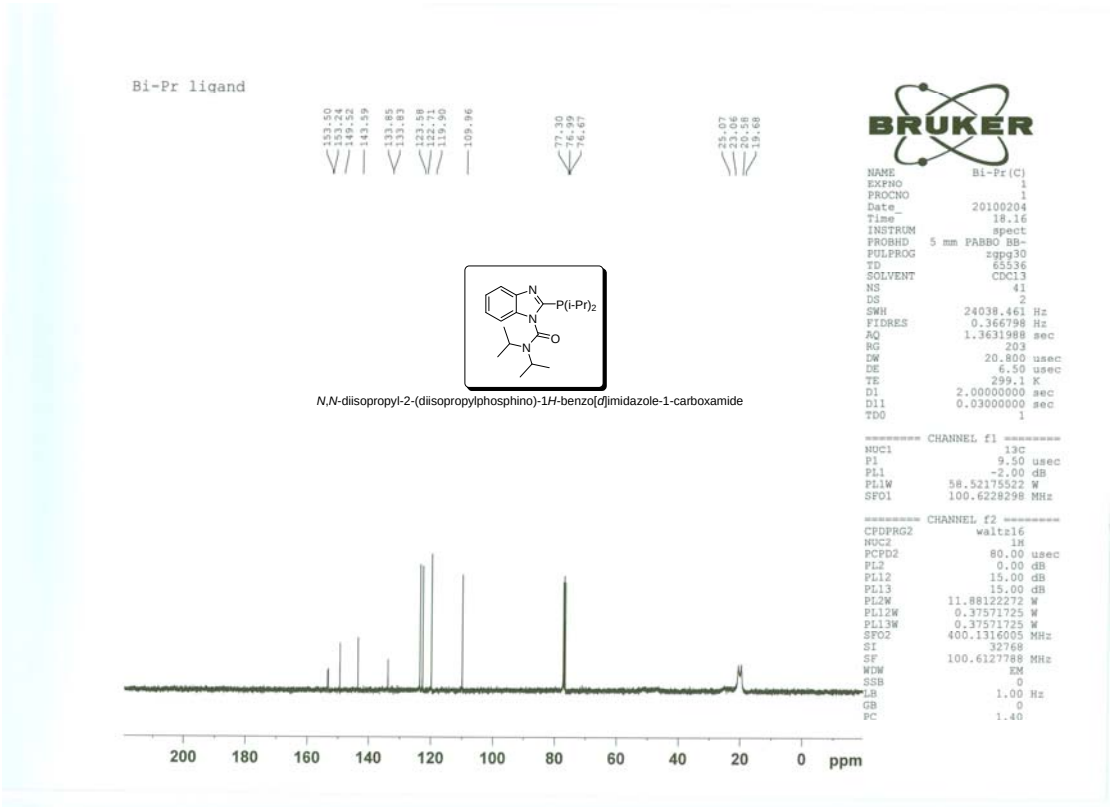
2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



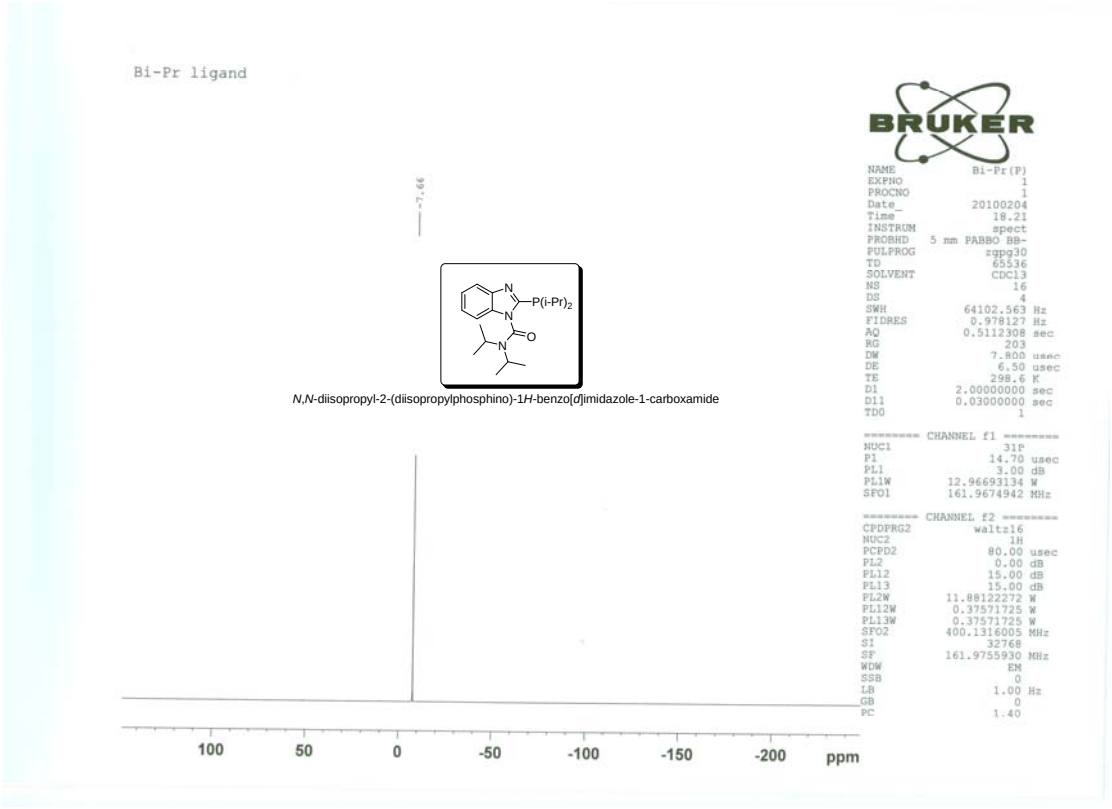
^{1}H NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide



^{13}C NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide

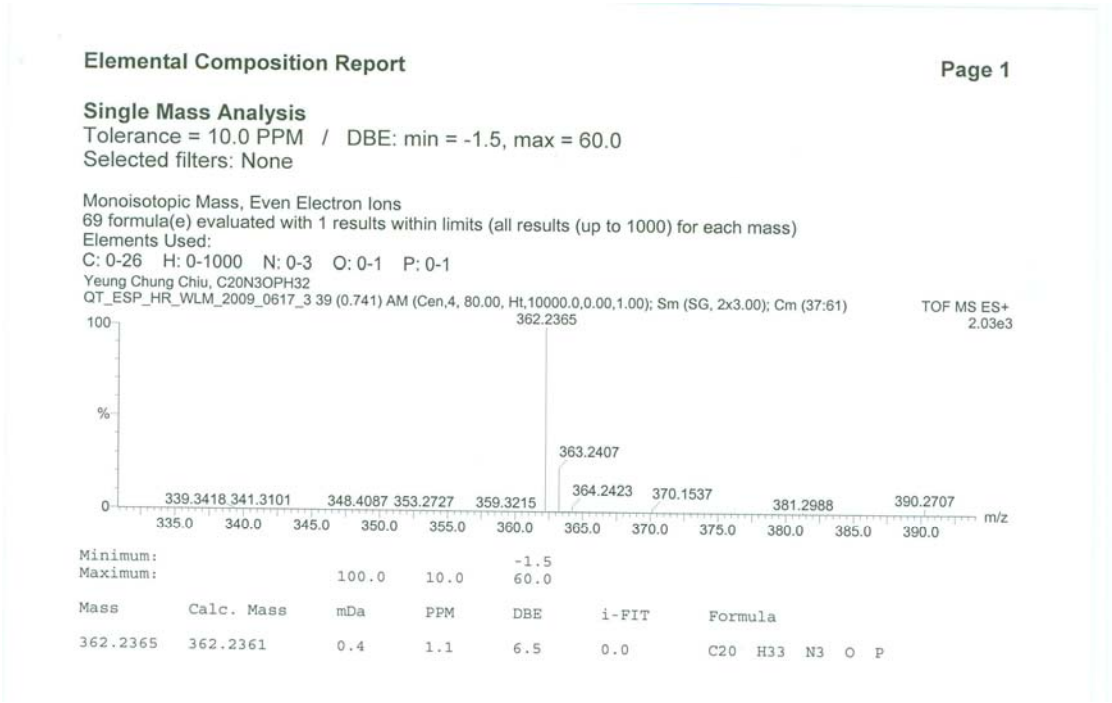


^{31}P NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide

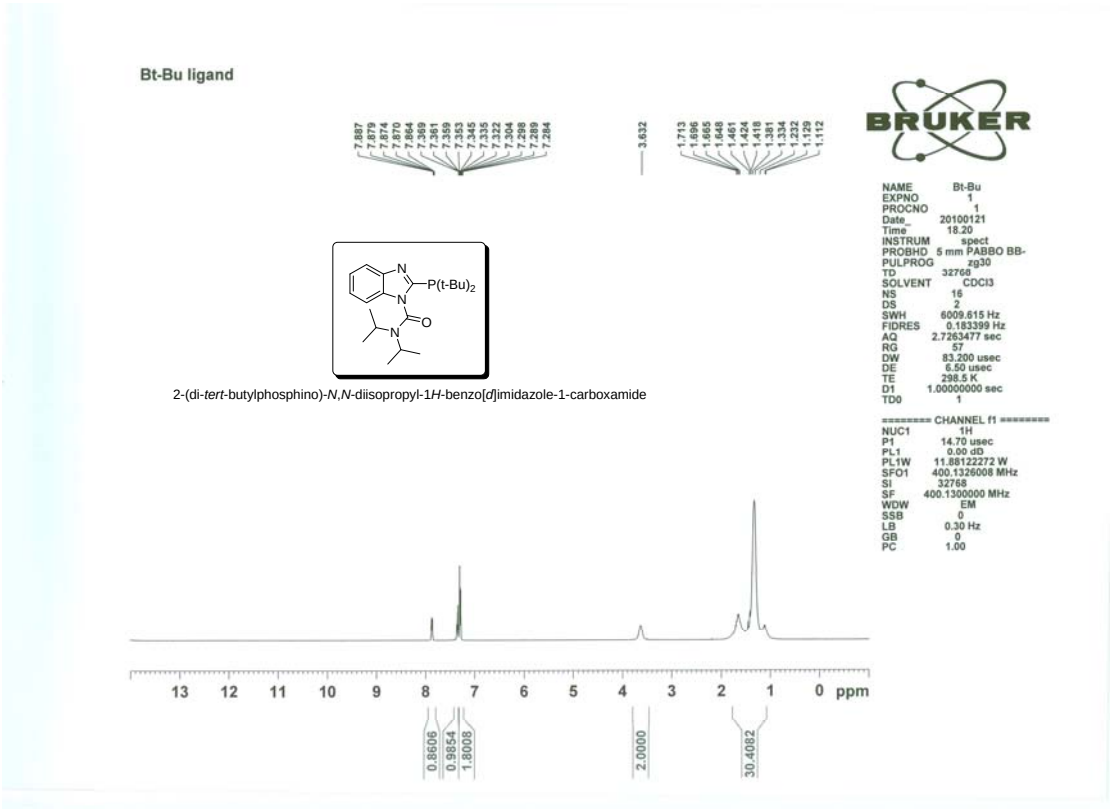


High resolution mass spectrum of

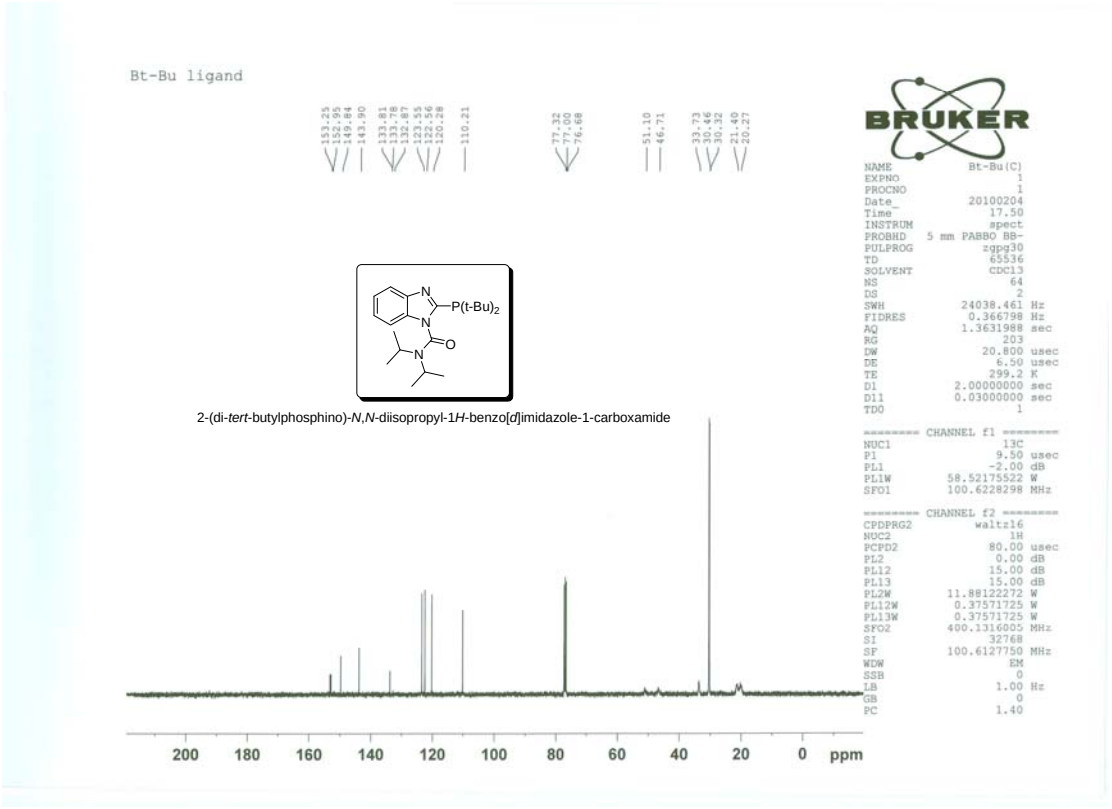
N,*N*-diisopropyl-2-(diisopropylphosphino)-1H-benzo[d]imidazole-1-carboxamide



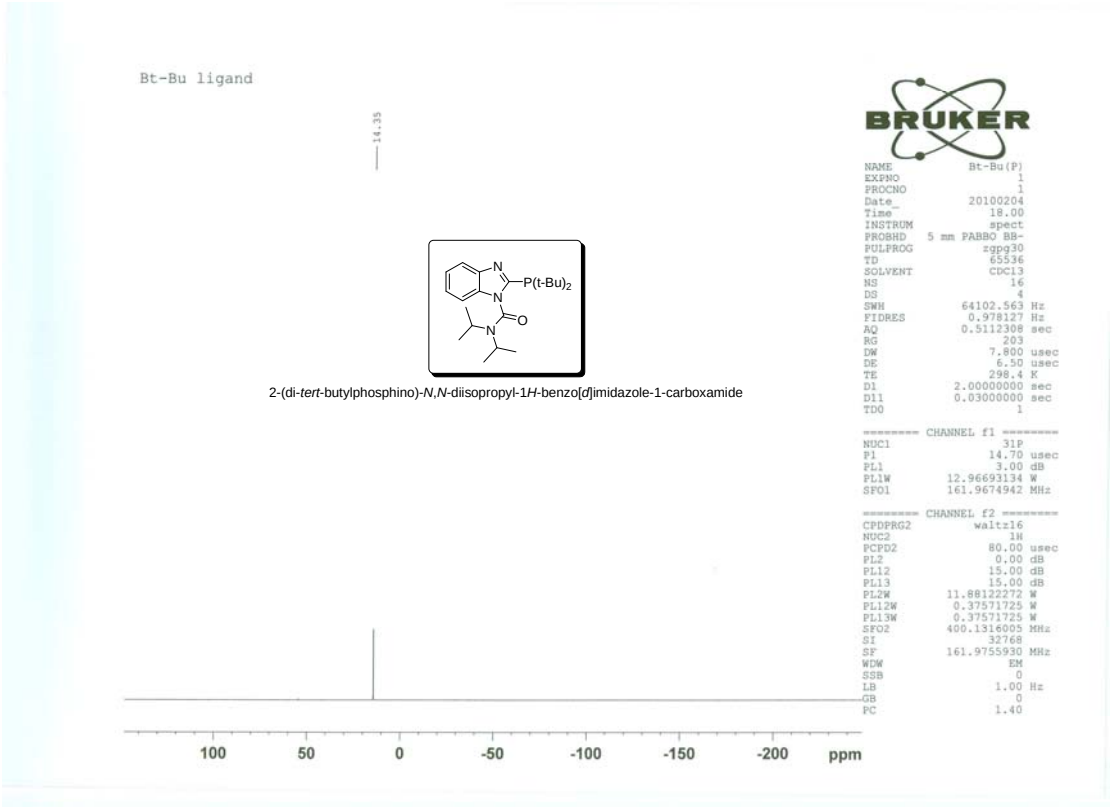
^{1}H NMR of 2-(di-*tert*-butylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



^{13}C NMR of 2-(di-*tert*-butylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

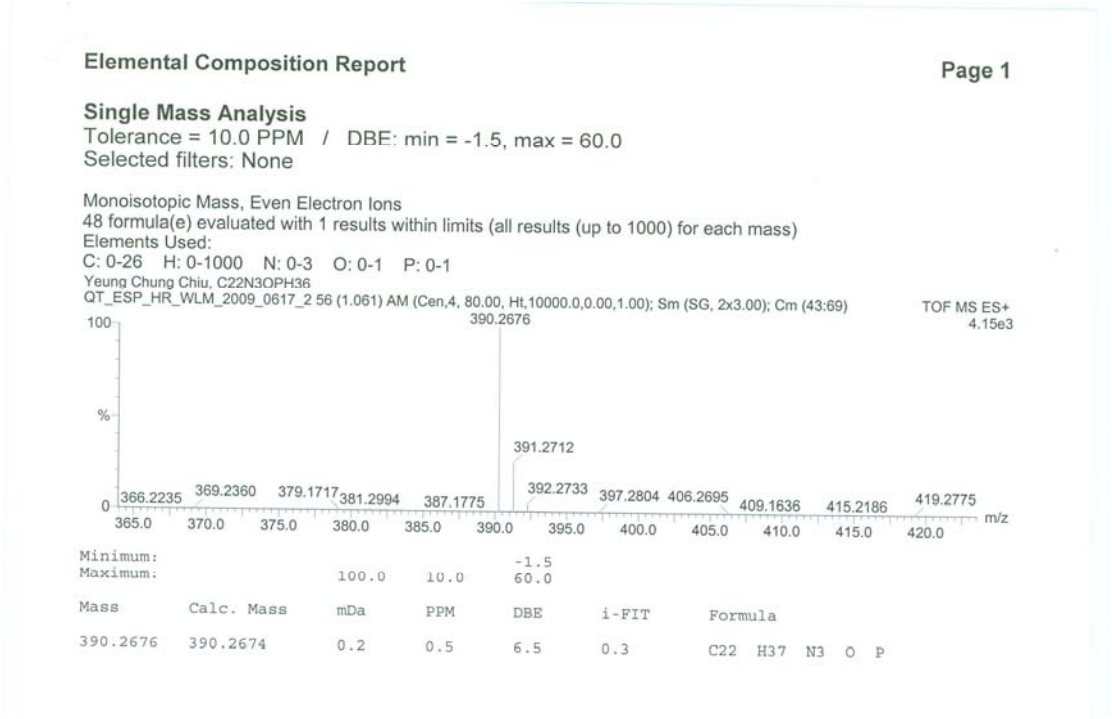


^{31}P NMR of 2-(di-*tert*-butylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

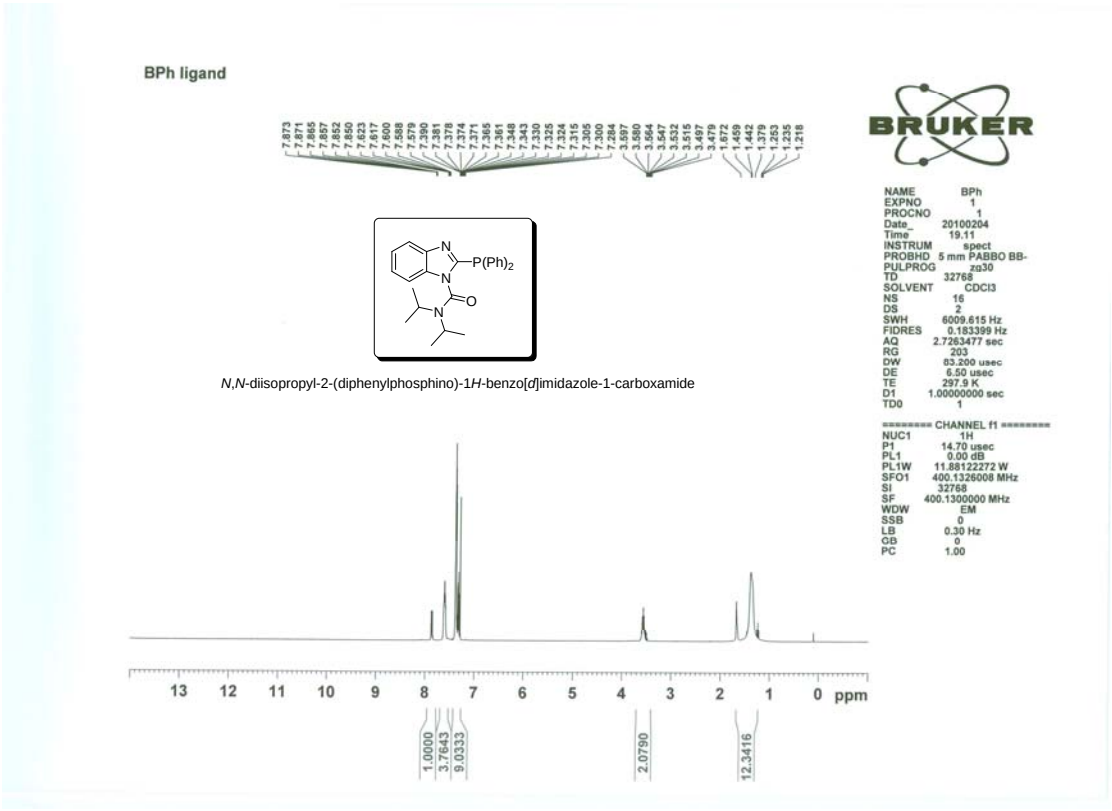


High resolution mass spectrum of

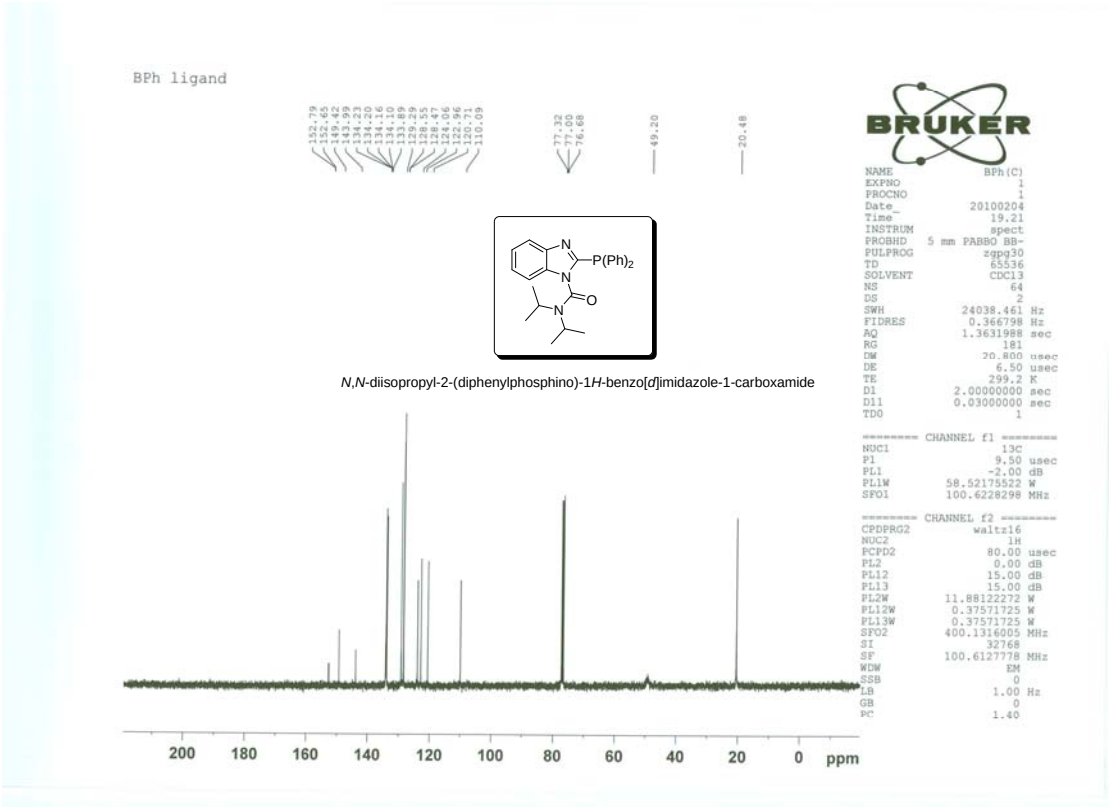
2-(di-*tert*-butylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



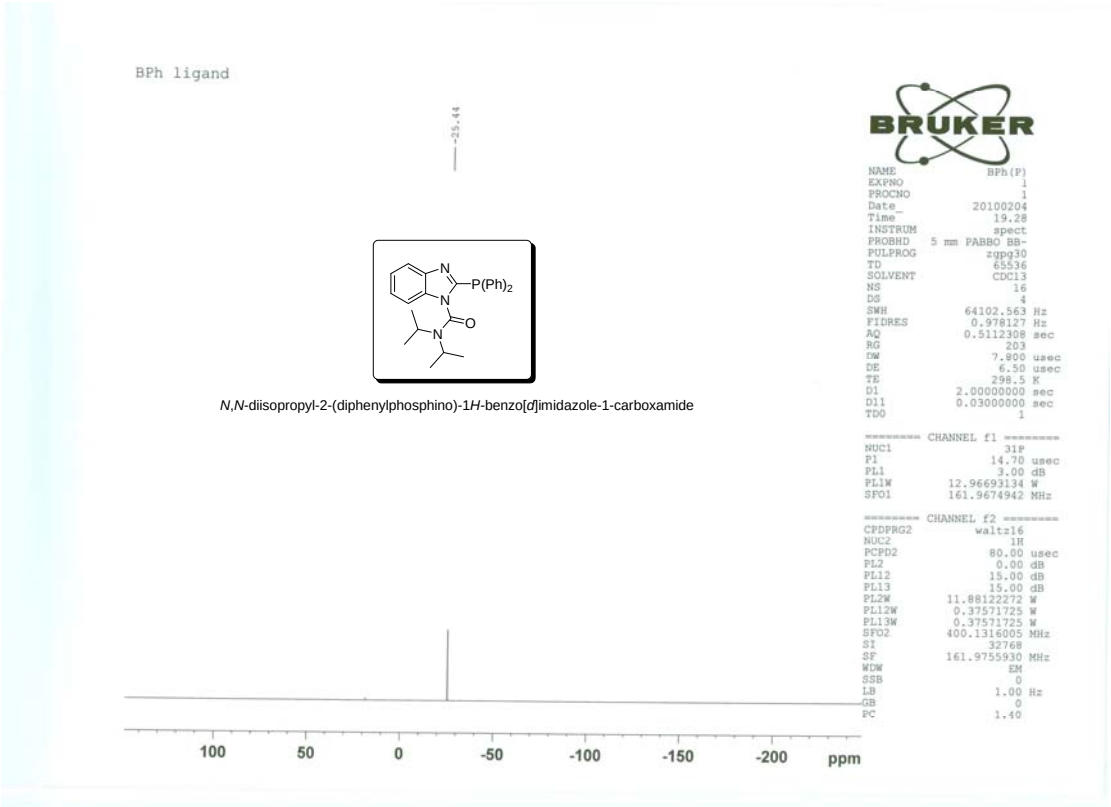
^{1}H NMR of *N*,*N*-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



^{13}C NMR of *N*,*N*-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



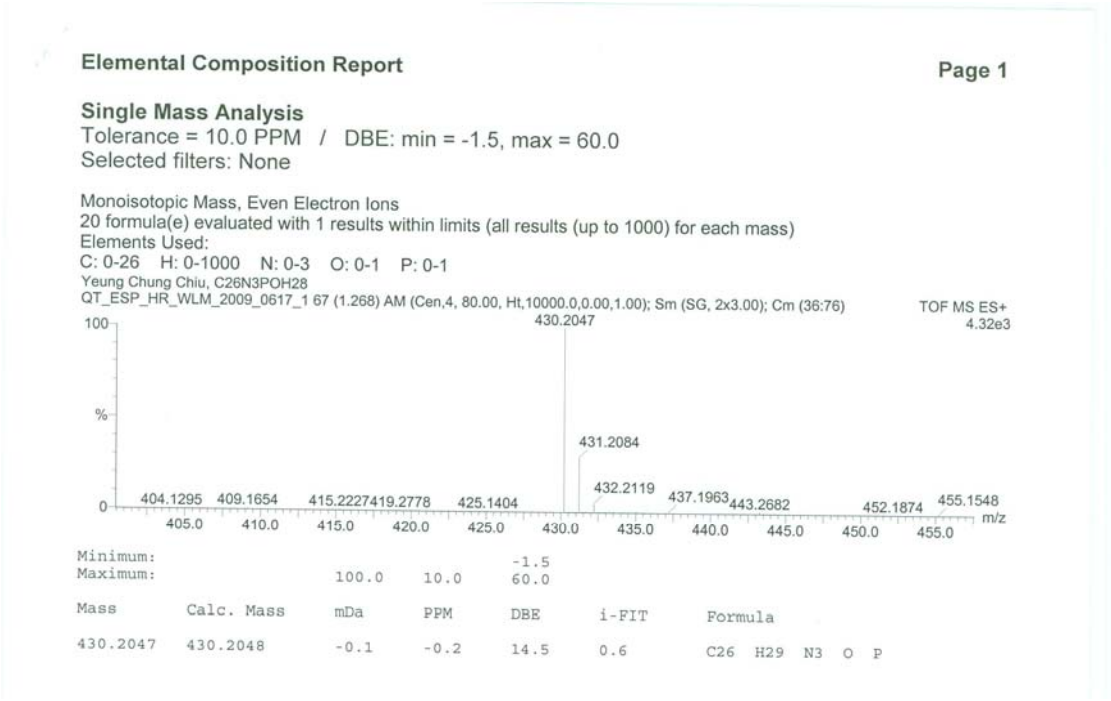
^{31}P NMR of *N*,*N*-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



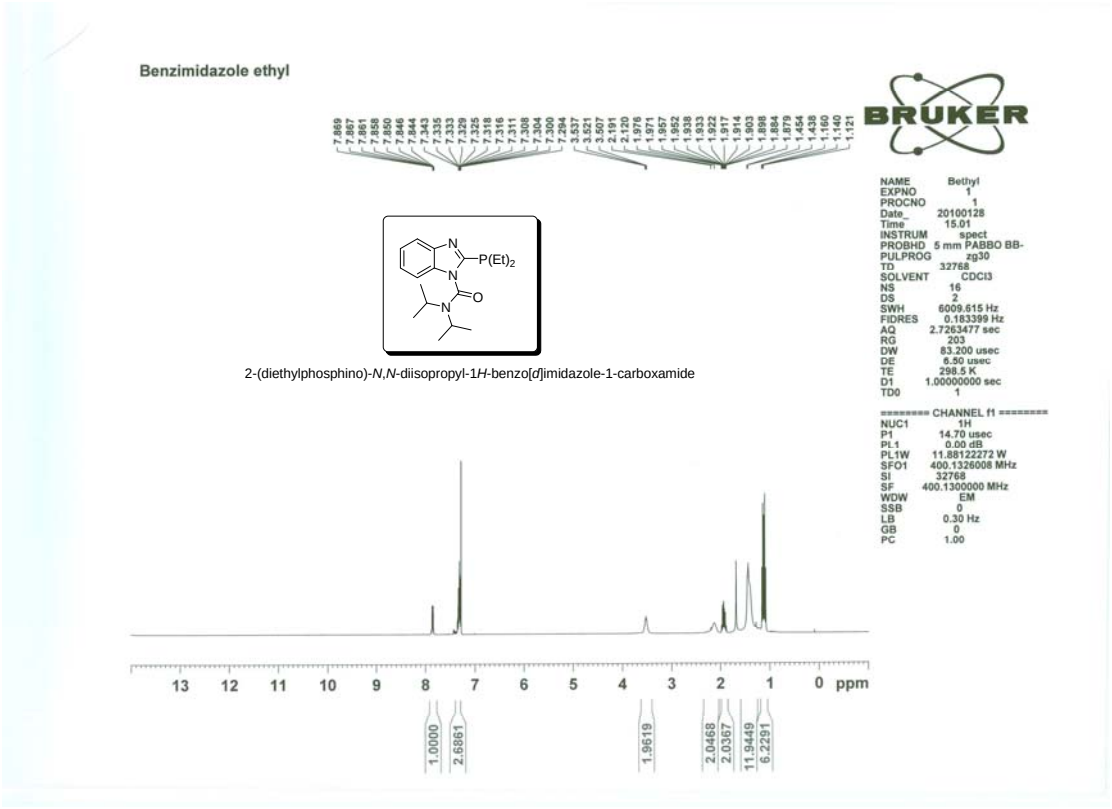
N,*N*-diisopropyl-2-(diphenylphosphino)-1*H*-benzo[*d*]imidazole-1-carboxamide

High resolution mass spectrum of

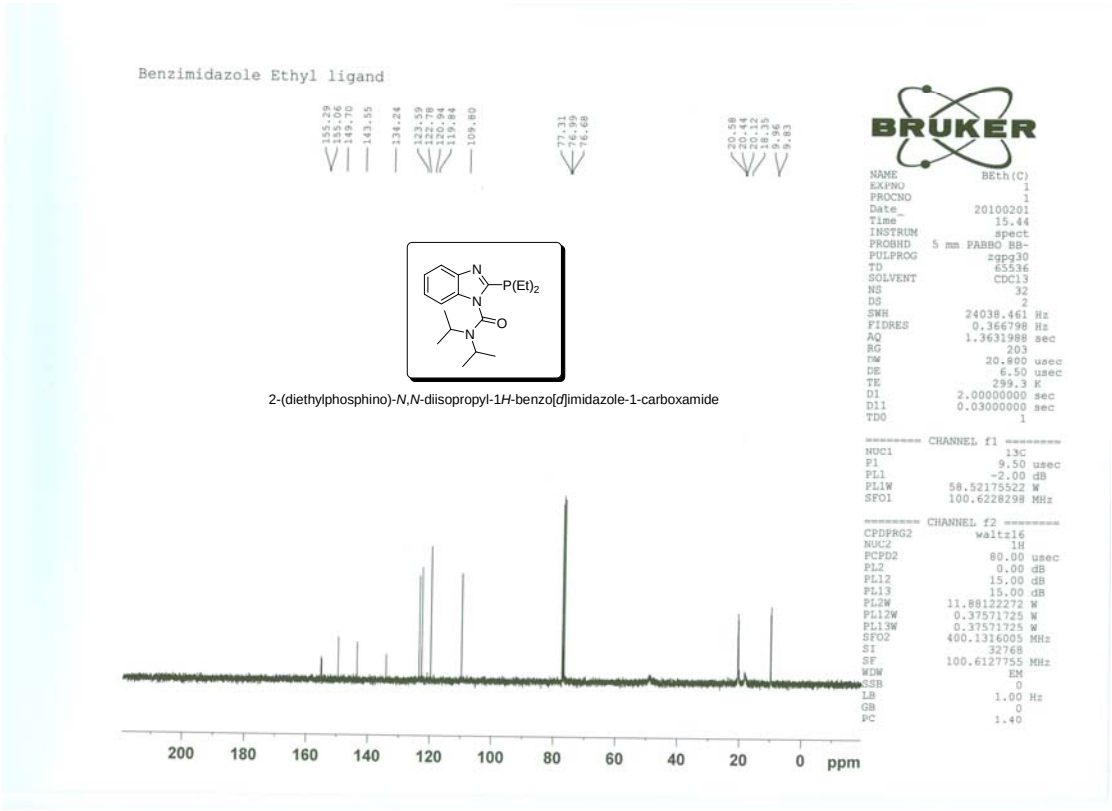
N,*N*-diisopropyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



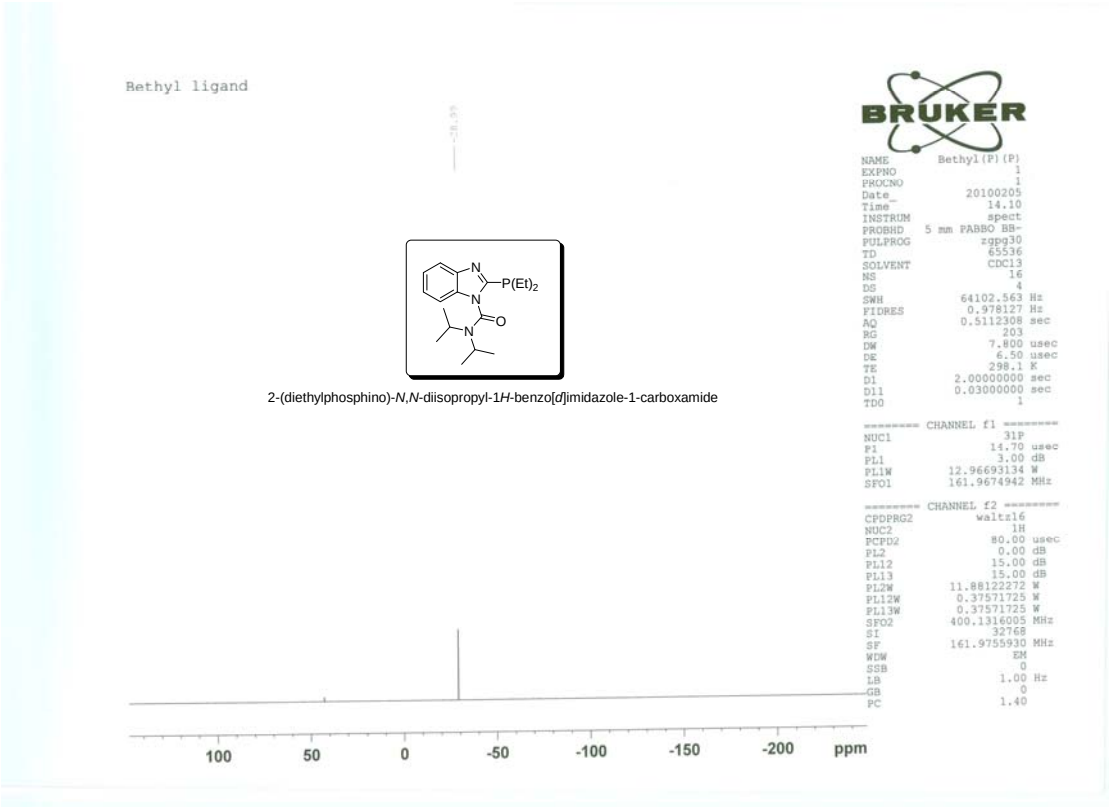
^{1}H NMR of 2-(diethylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



^{13}C NMR of 2-(diethylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

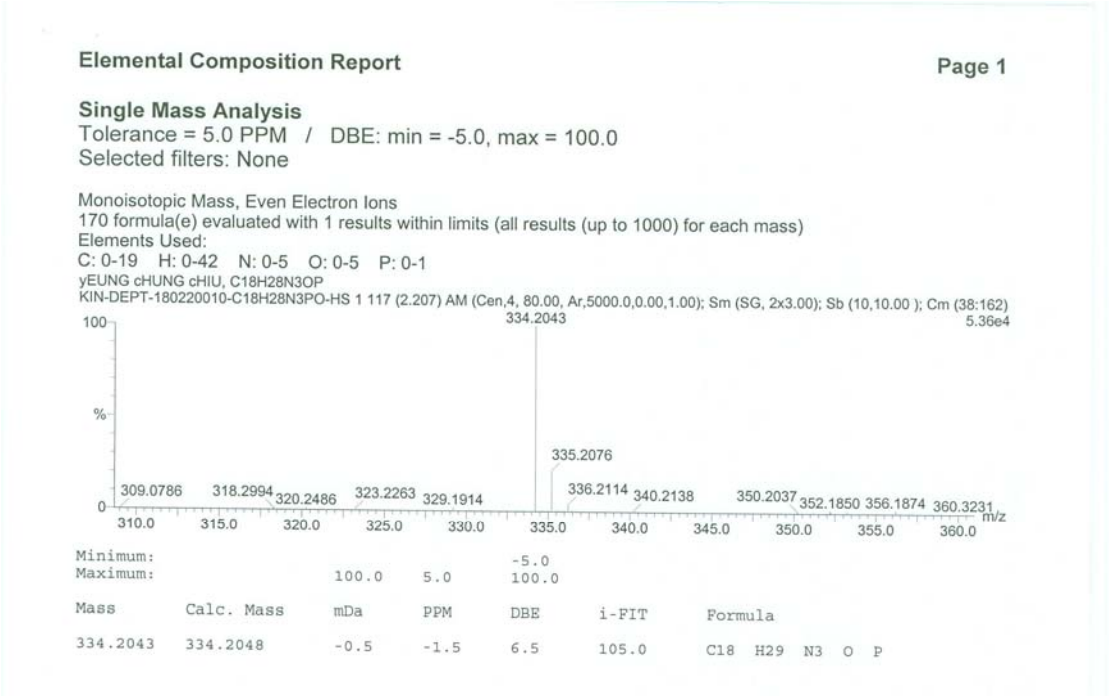


^{31}P NMR of 2-(diethylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

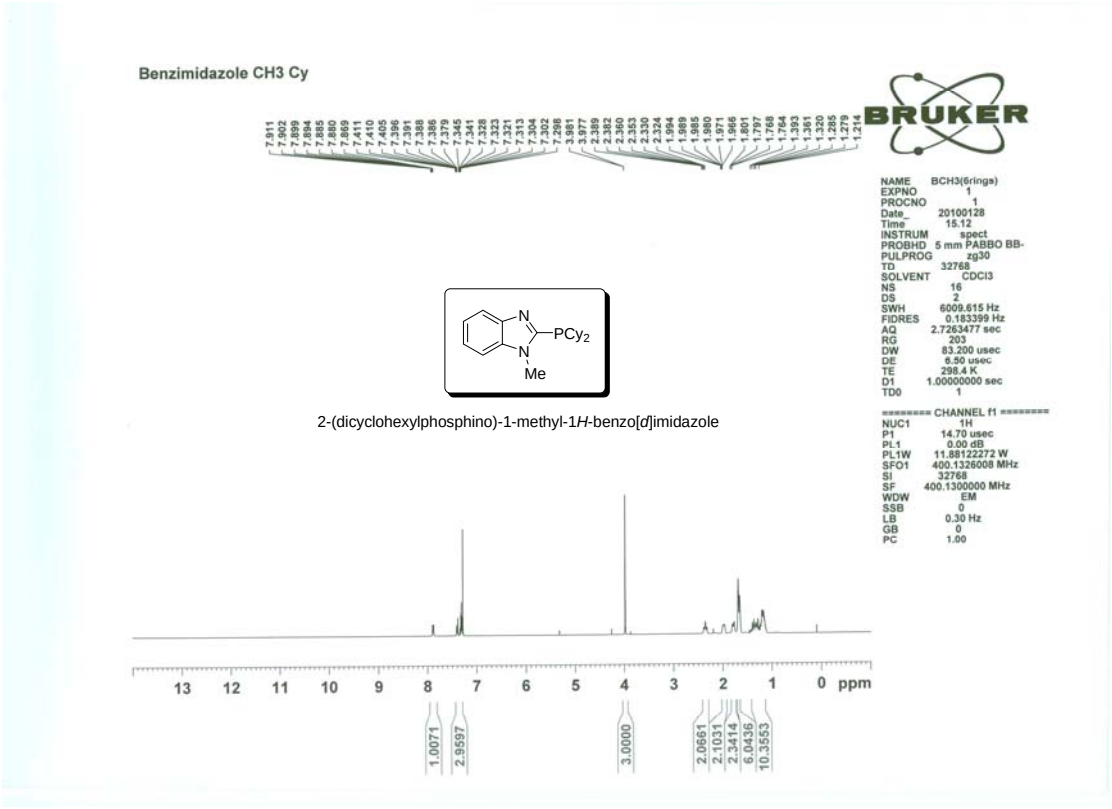


High resolution mass spectrum of

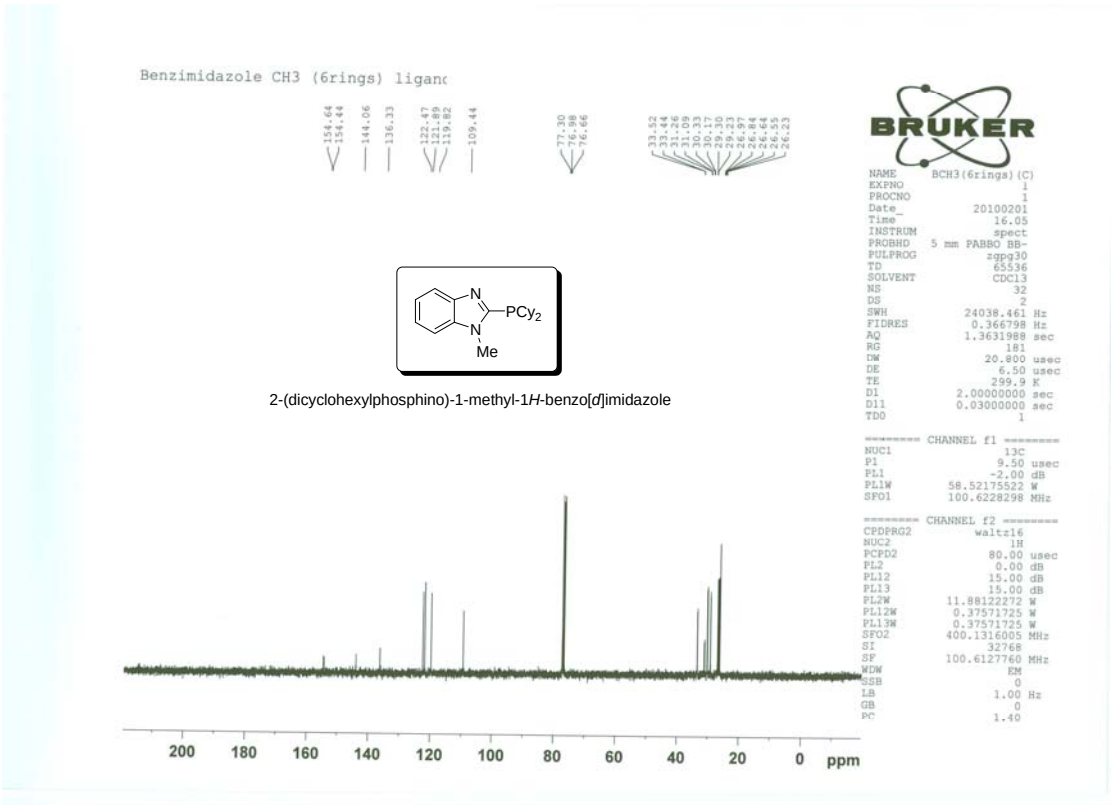
2-(diethylphosphino)-*N*,*N*-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



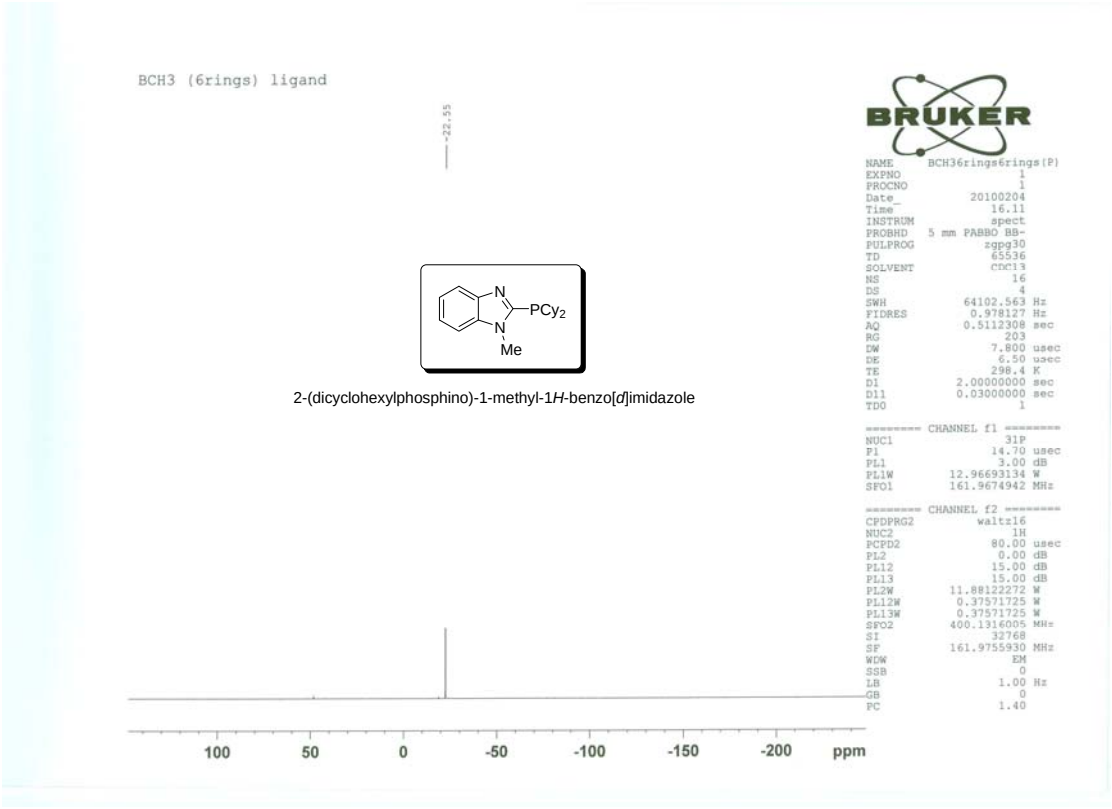
^{1}H NMR of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole



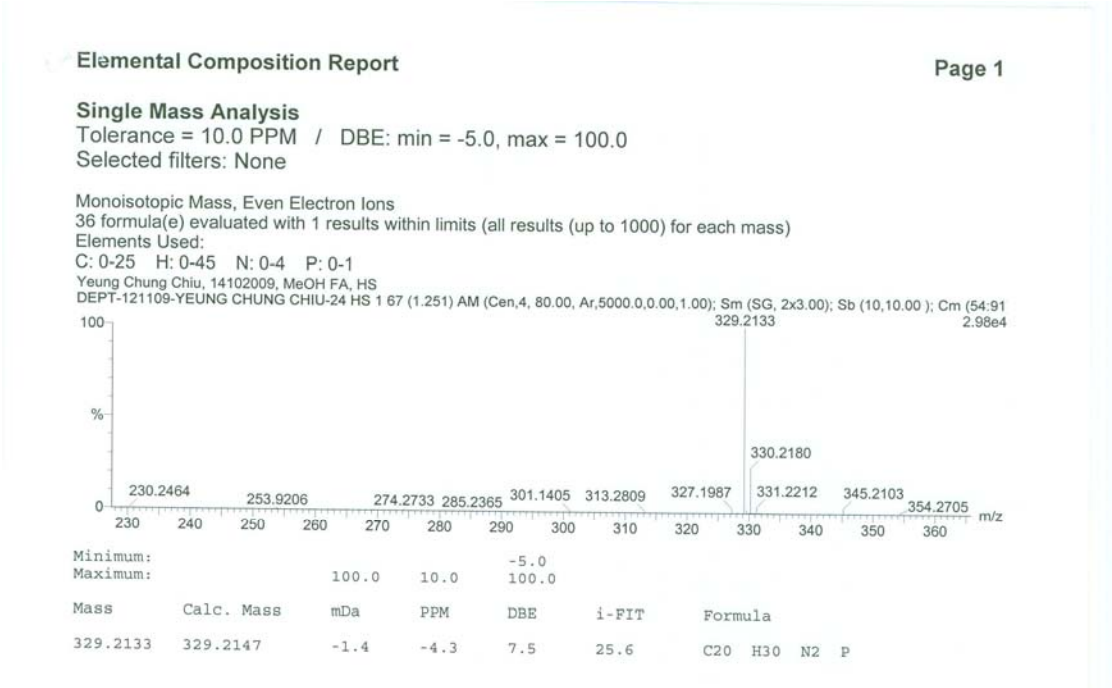
^{13}C NMR of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole



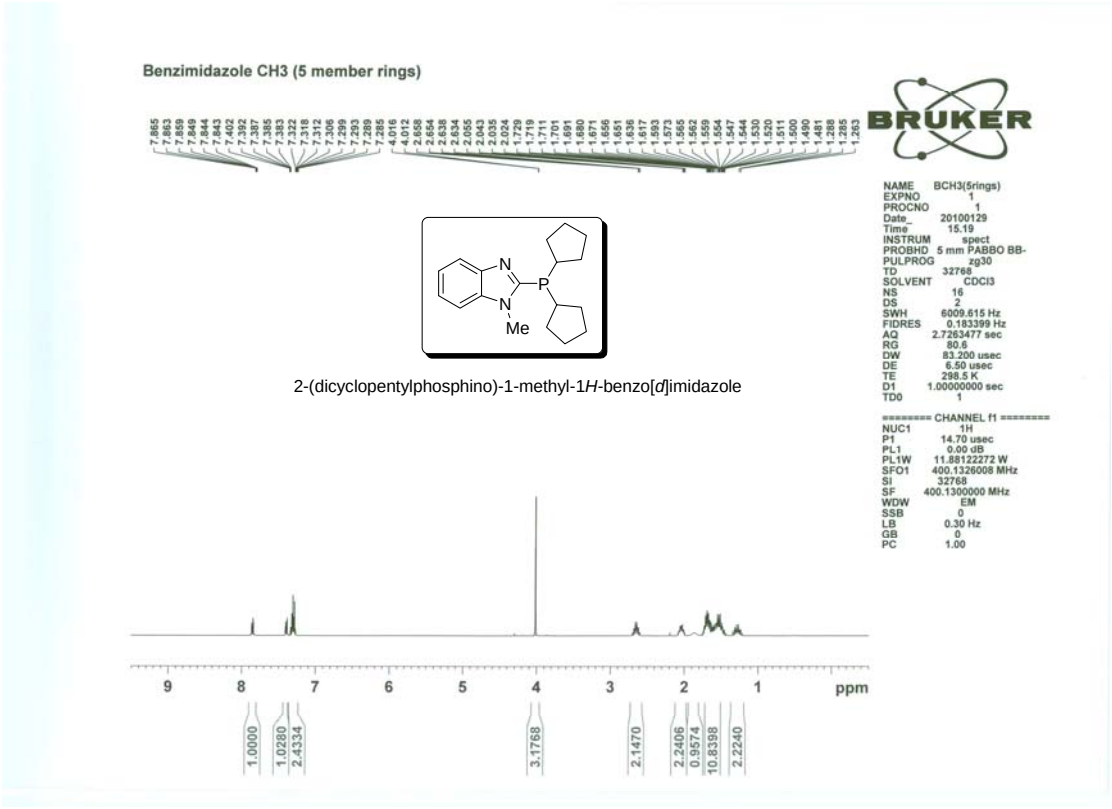
^{31}P NMR of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole



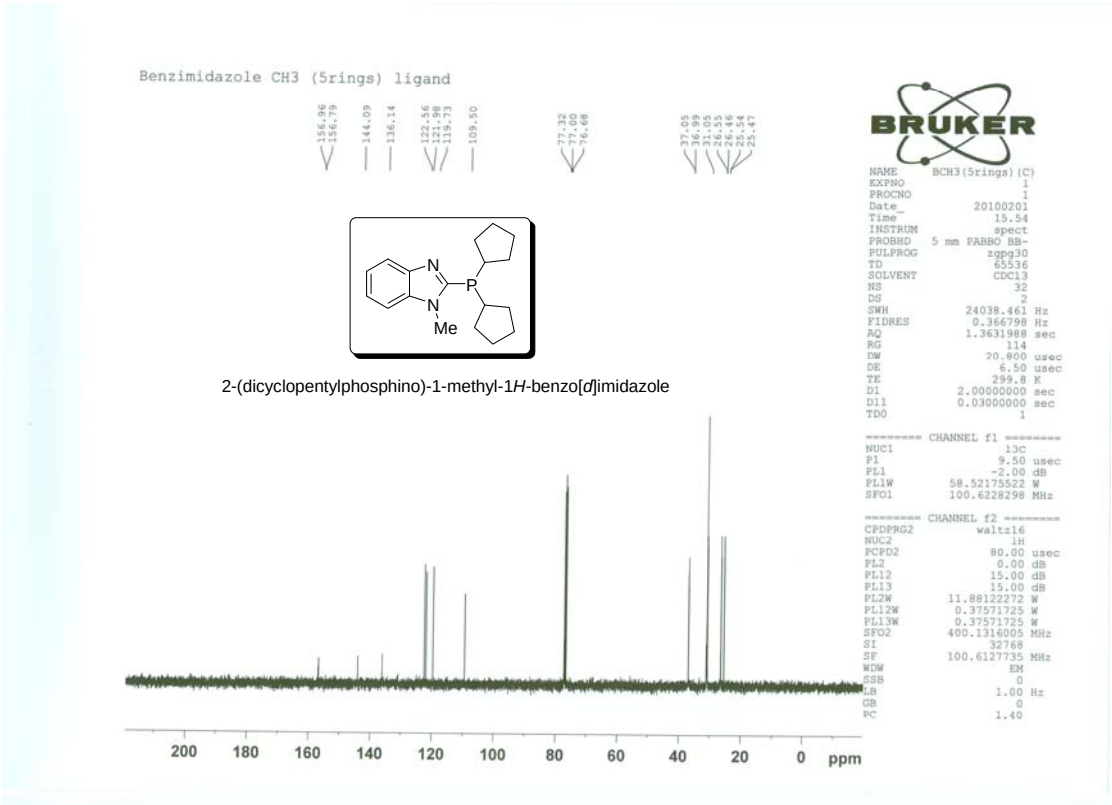
High resolution mass spectrum of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole



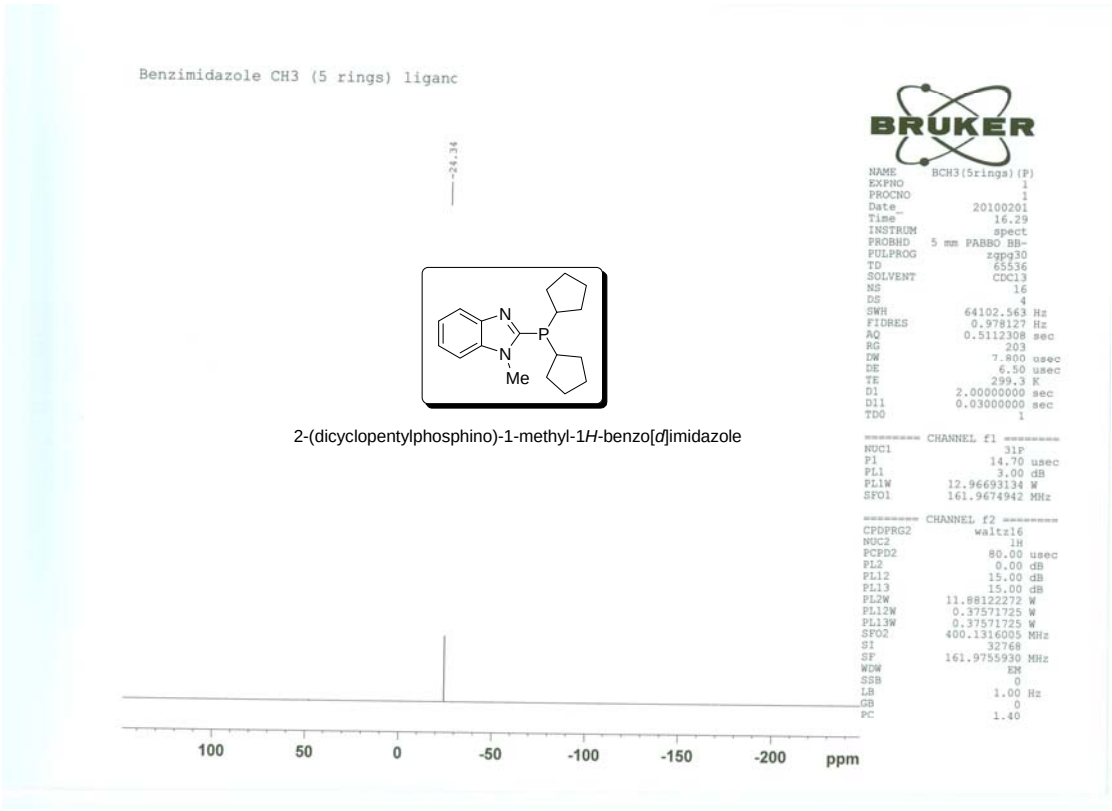
^{1}H NMR of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole



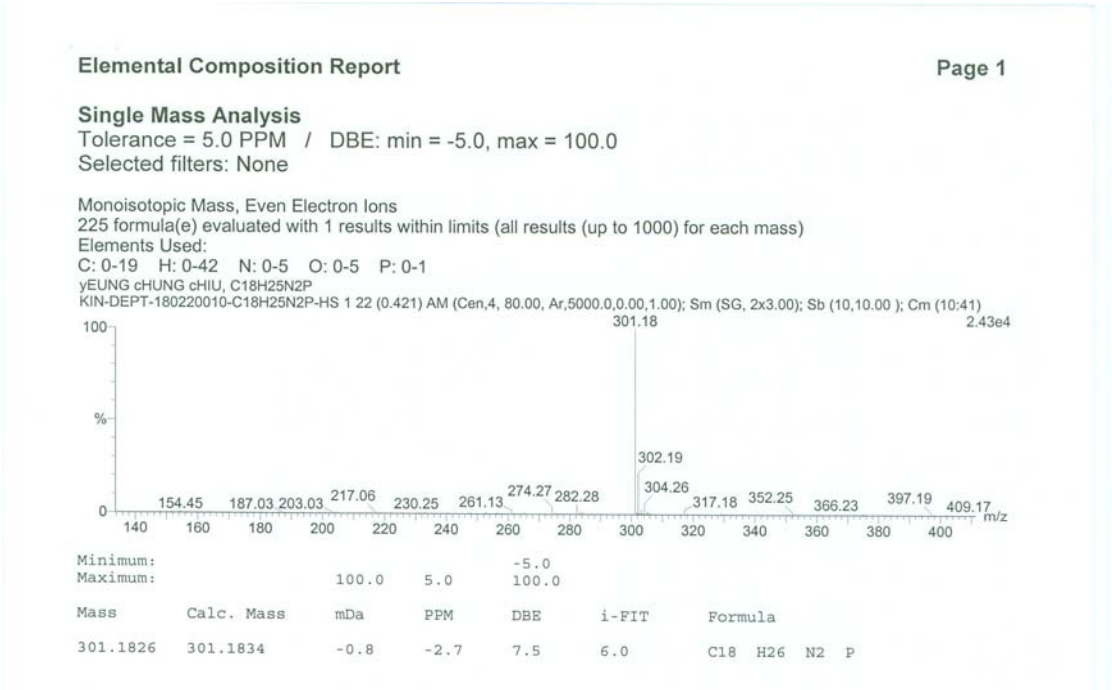
^{13}C NMR of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole



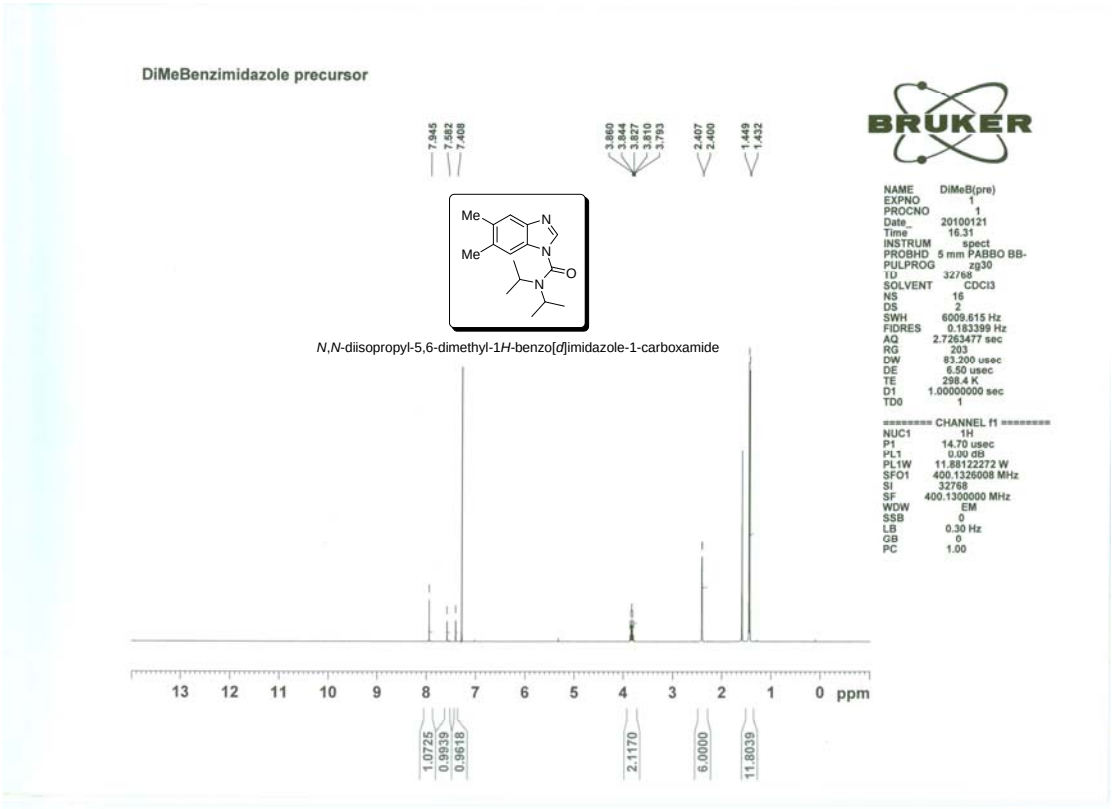
^{31}P NMR of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole



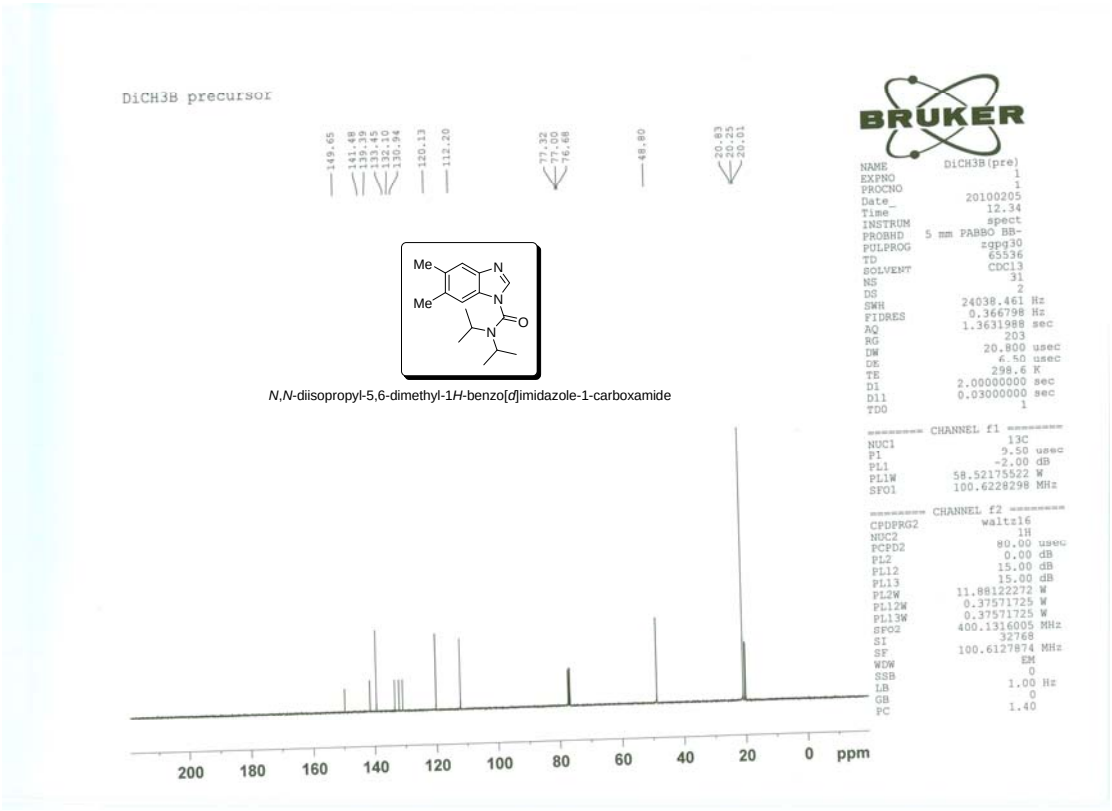
High resolution mass spectrum of 2-(dicyclopentylphosphino)-1-methyl-1H-benzo[d]imidazole



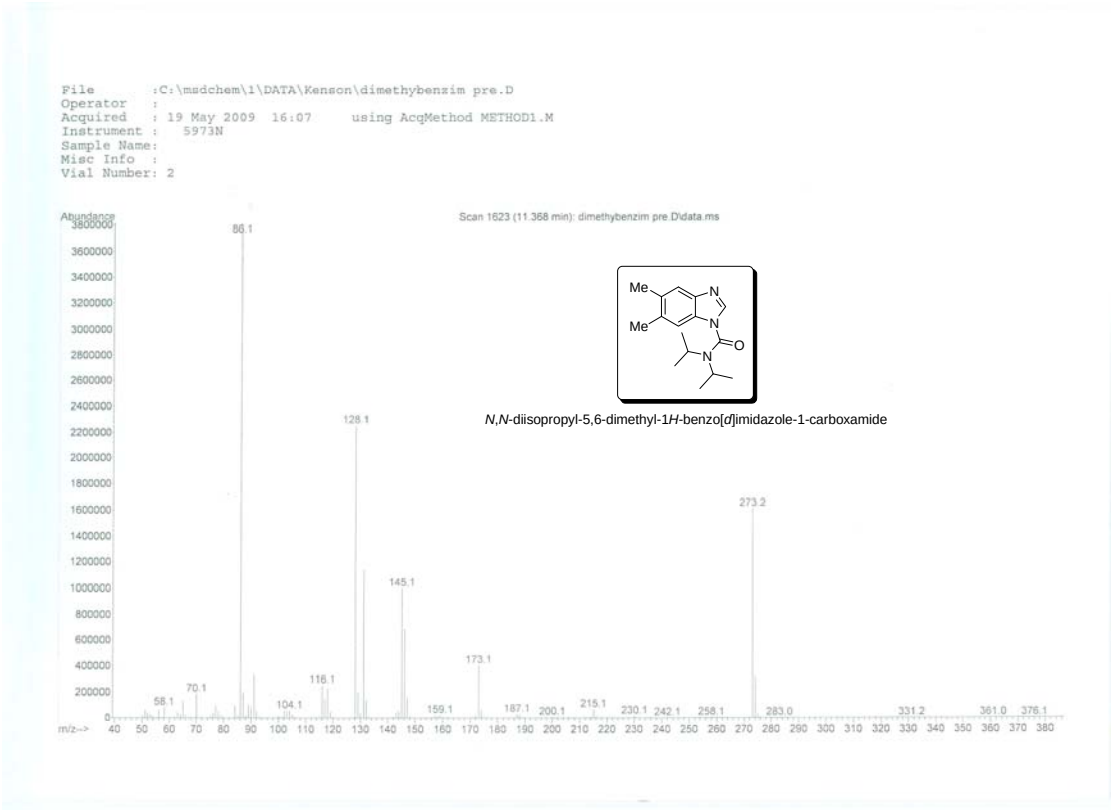
^{1}H NMR of *N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



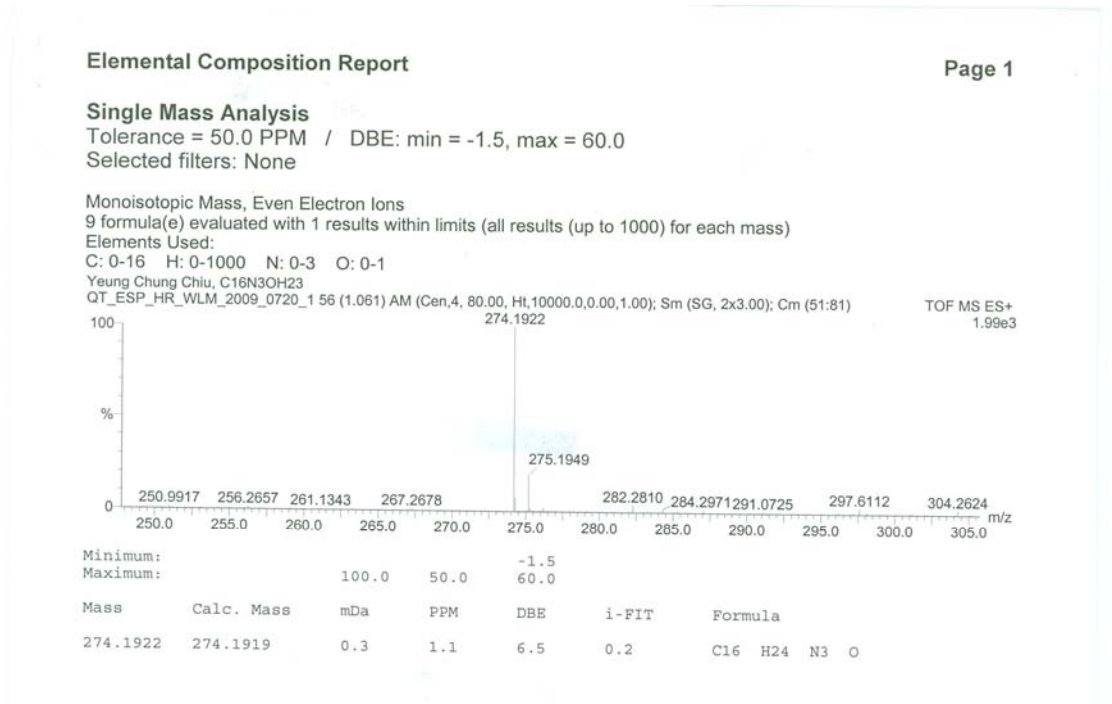
^{13}C NMR of *N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



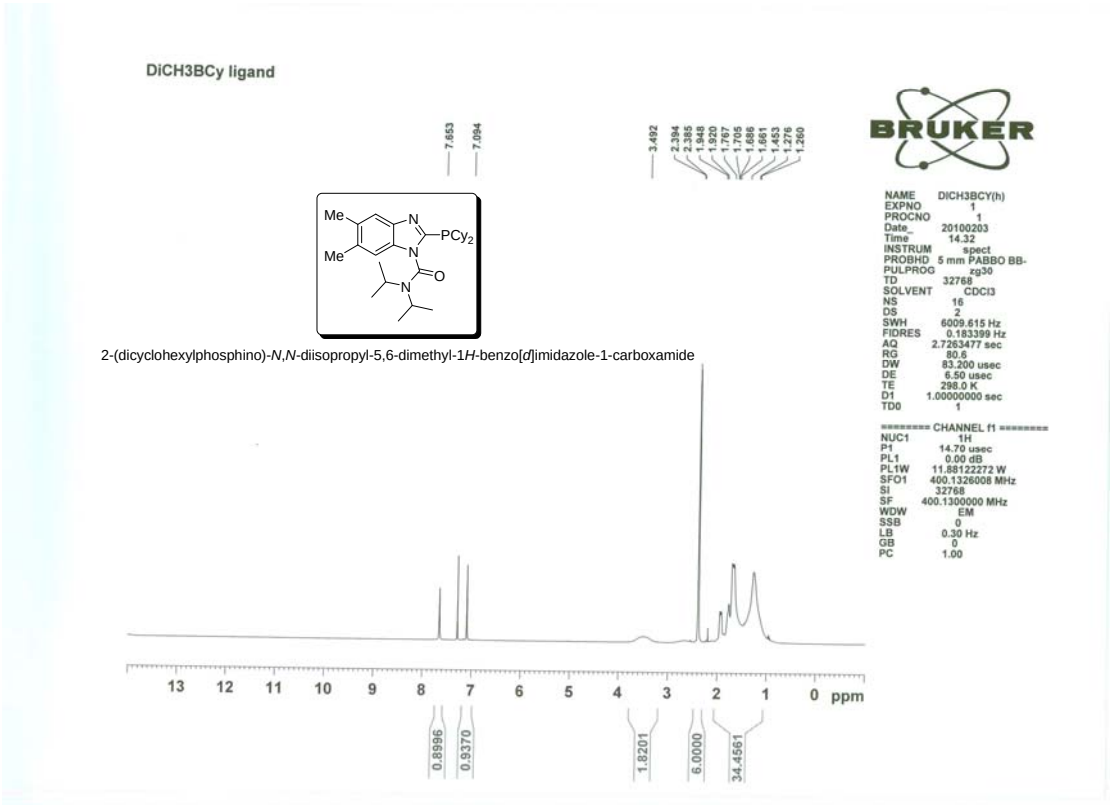
Mass spectrum of *N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



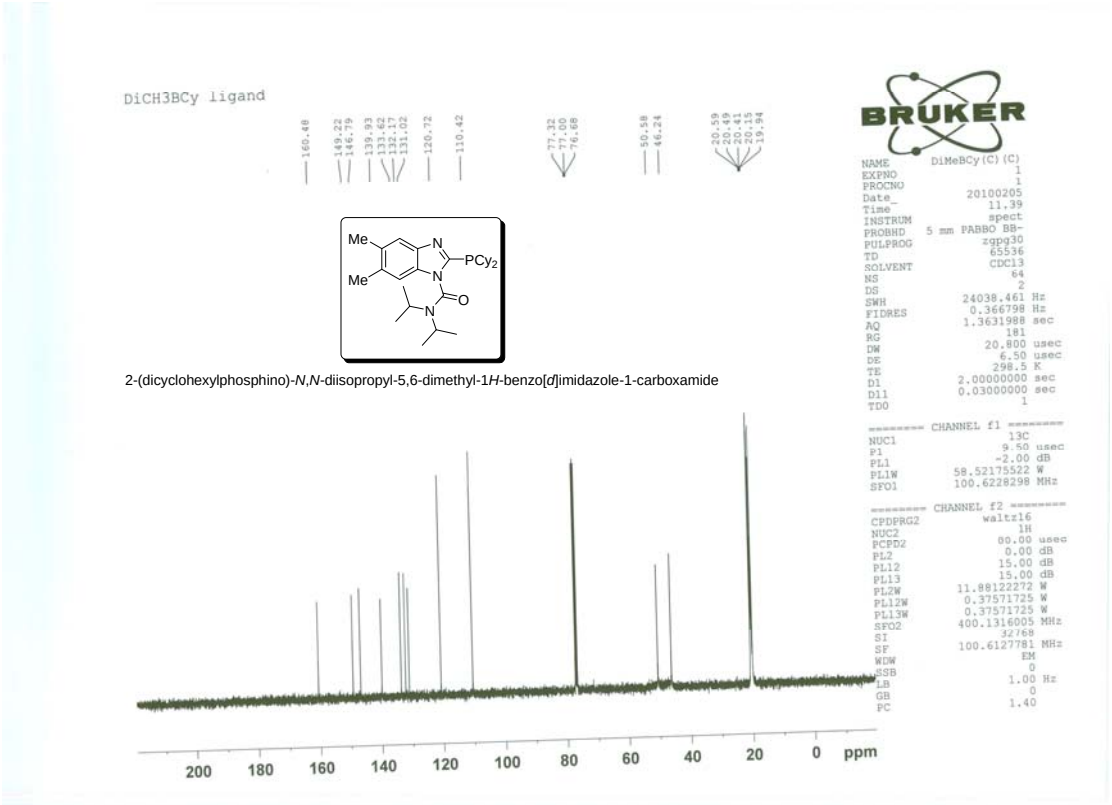
High resolution mass spectrum of *N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



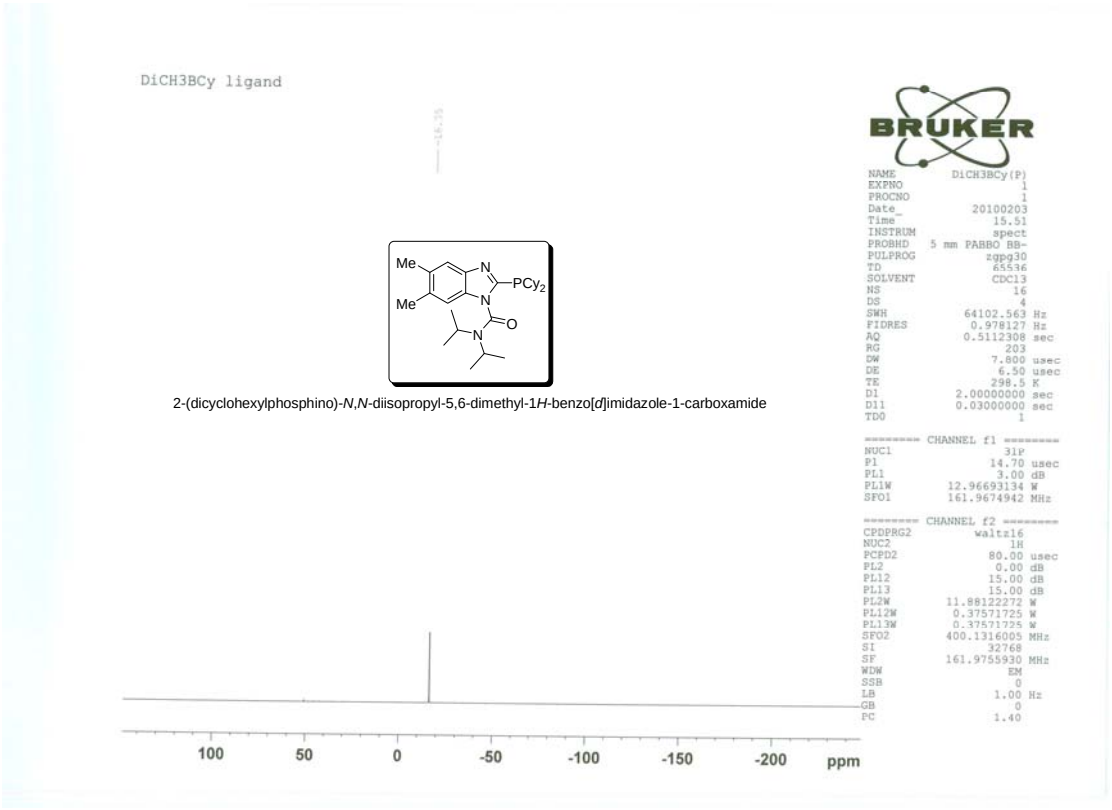
^{1}H NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



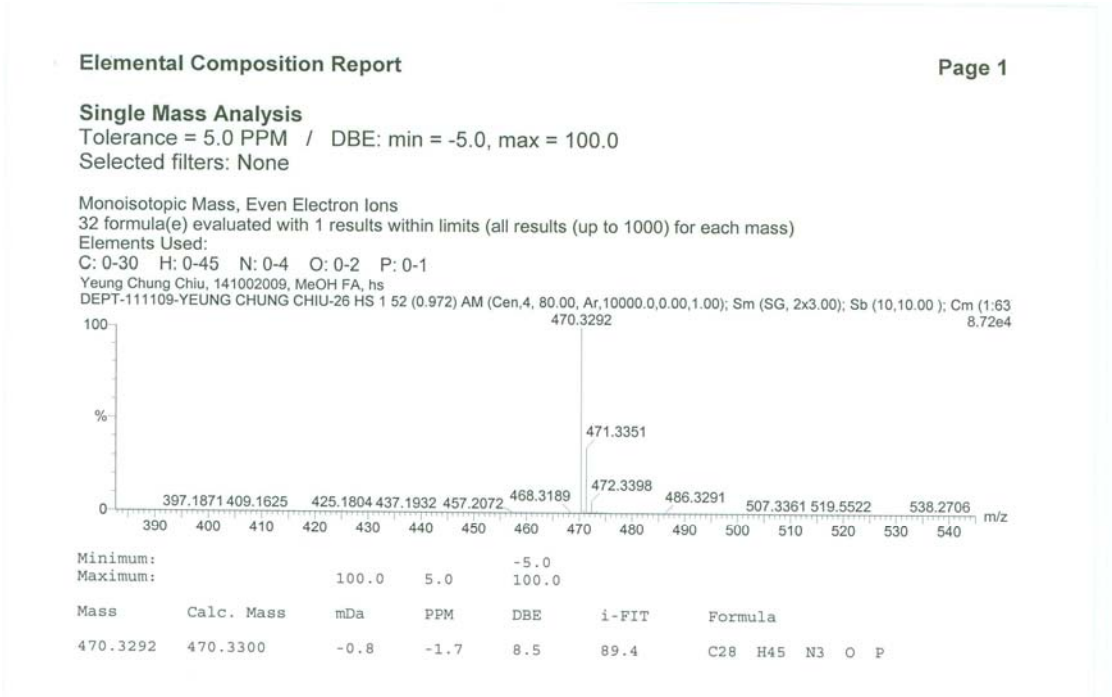
^{13}C NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



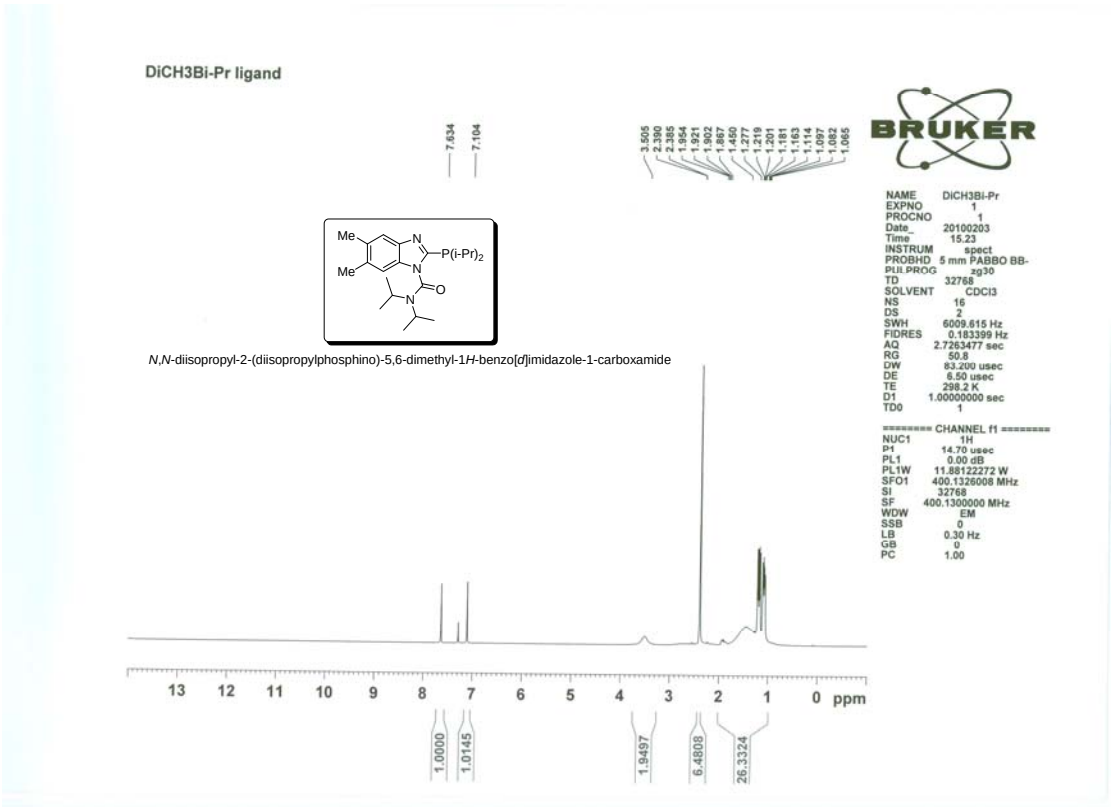
^{31}P NMR of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



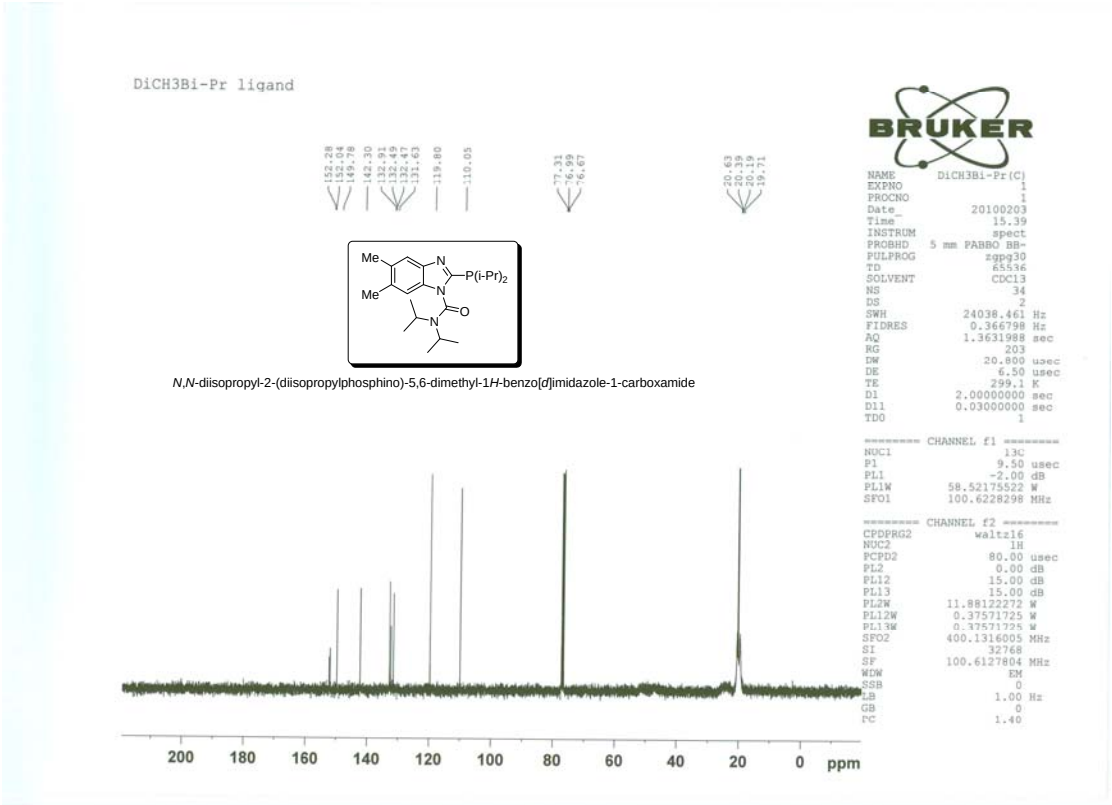
High resolution mass spectrum of 2-(dicyclohexylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



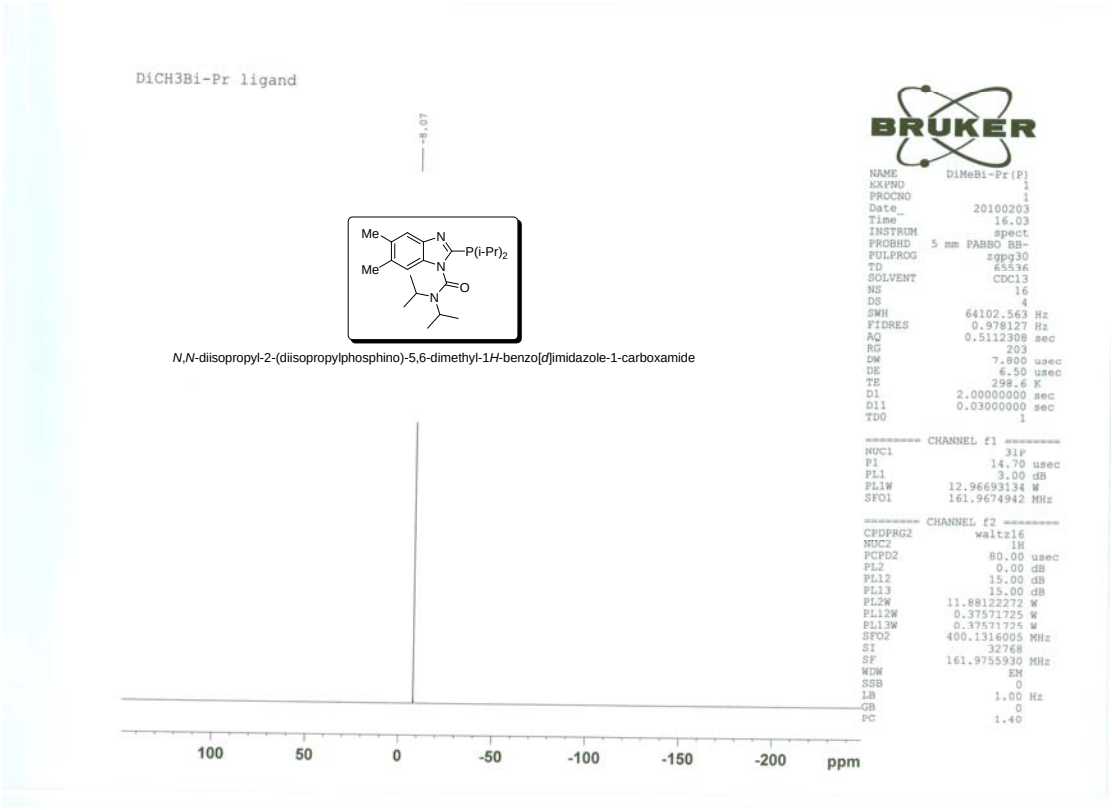
^{1}H NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



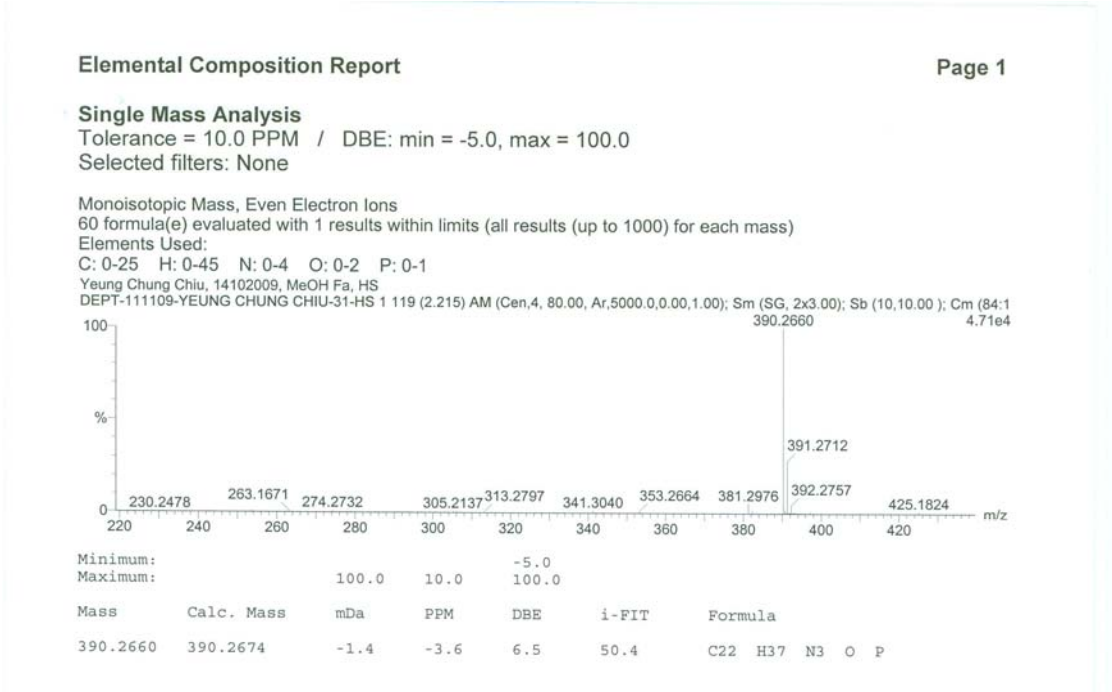
^{13}C NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



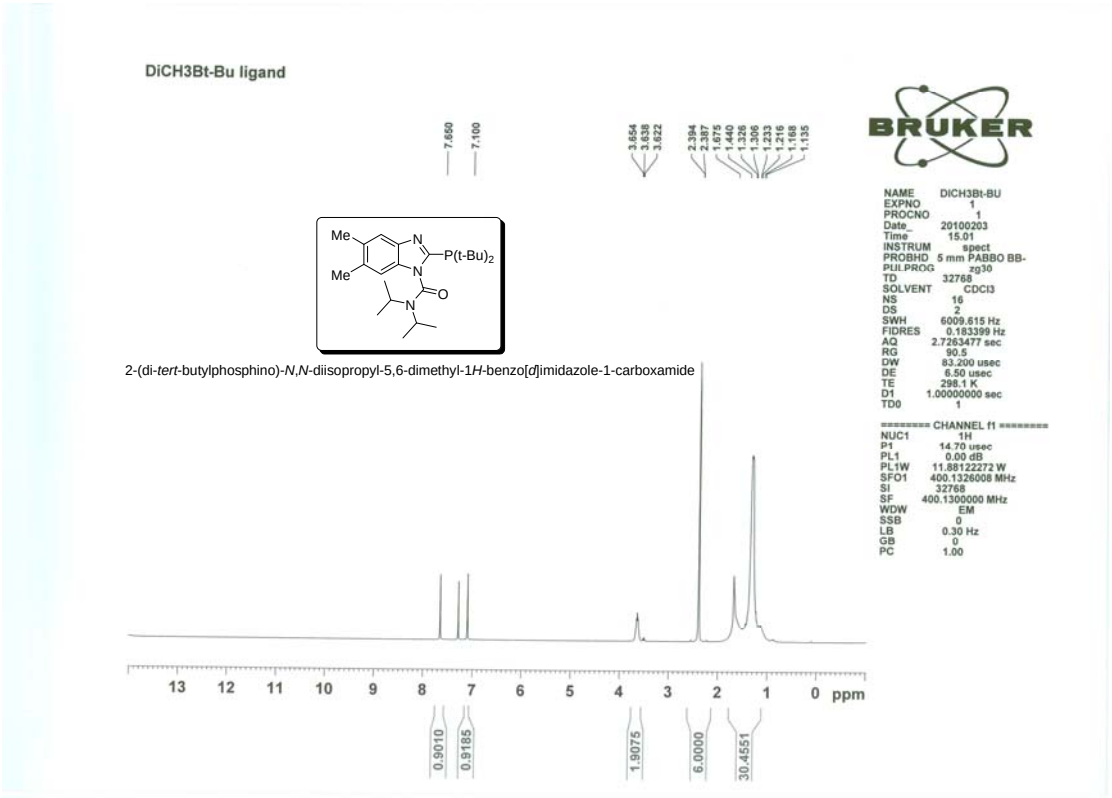
^{31}P NMR of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



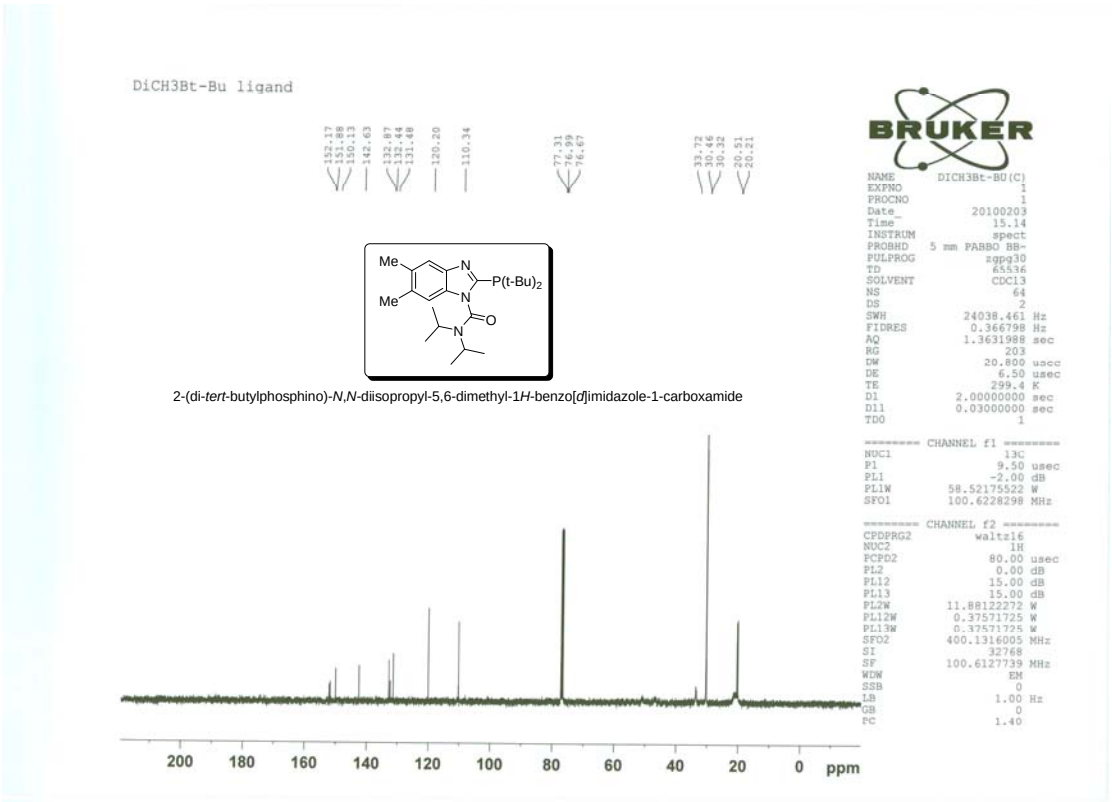
High resolution mass spectrum of *N*,*N*-diisopropyl-2-(diisopropylphosphino)-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



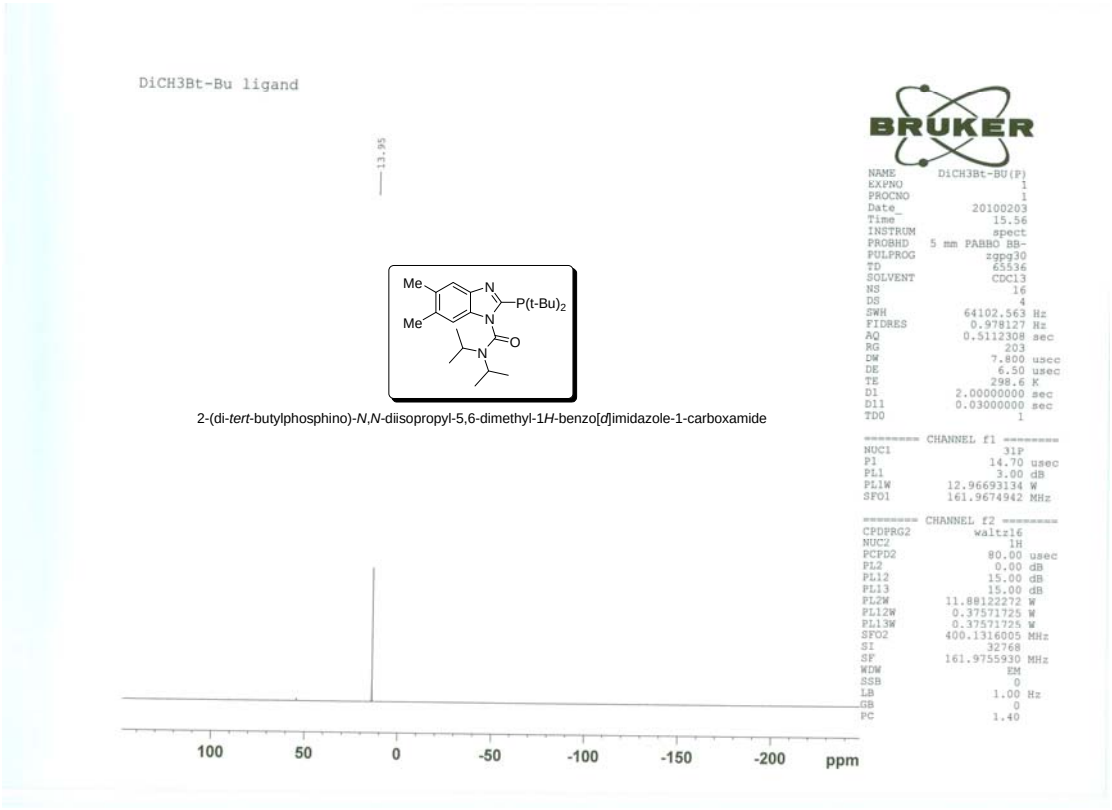
^{1}H NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



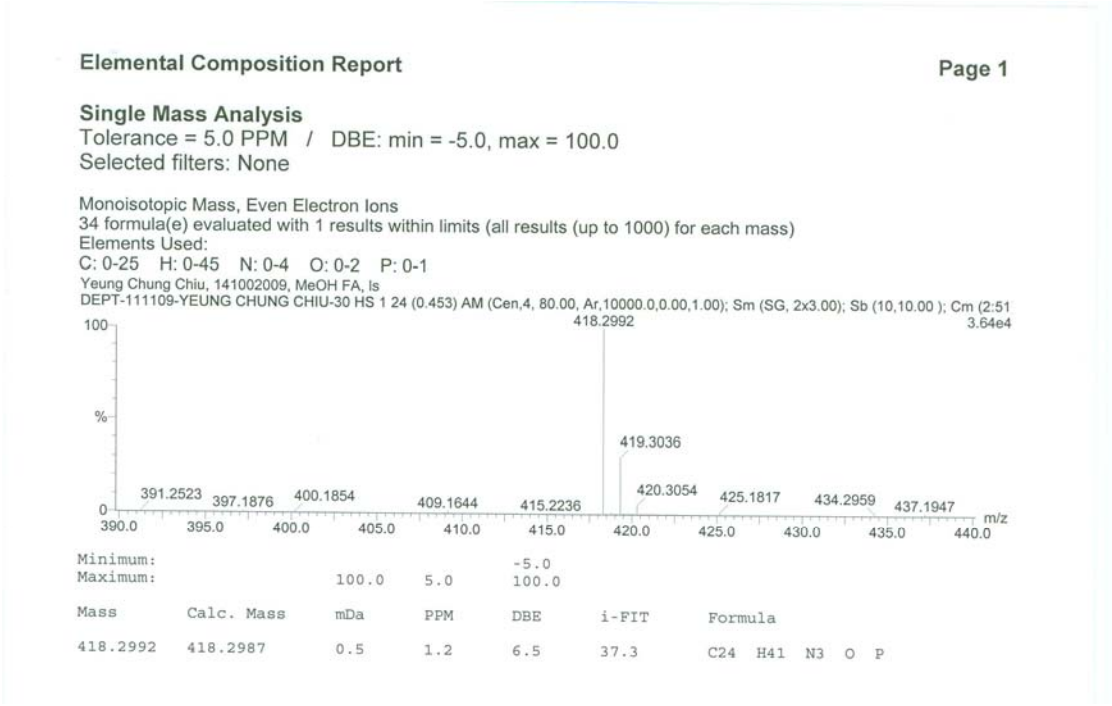
^{13}C NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



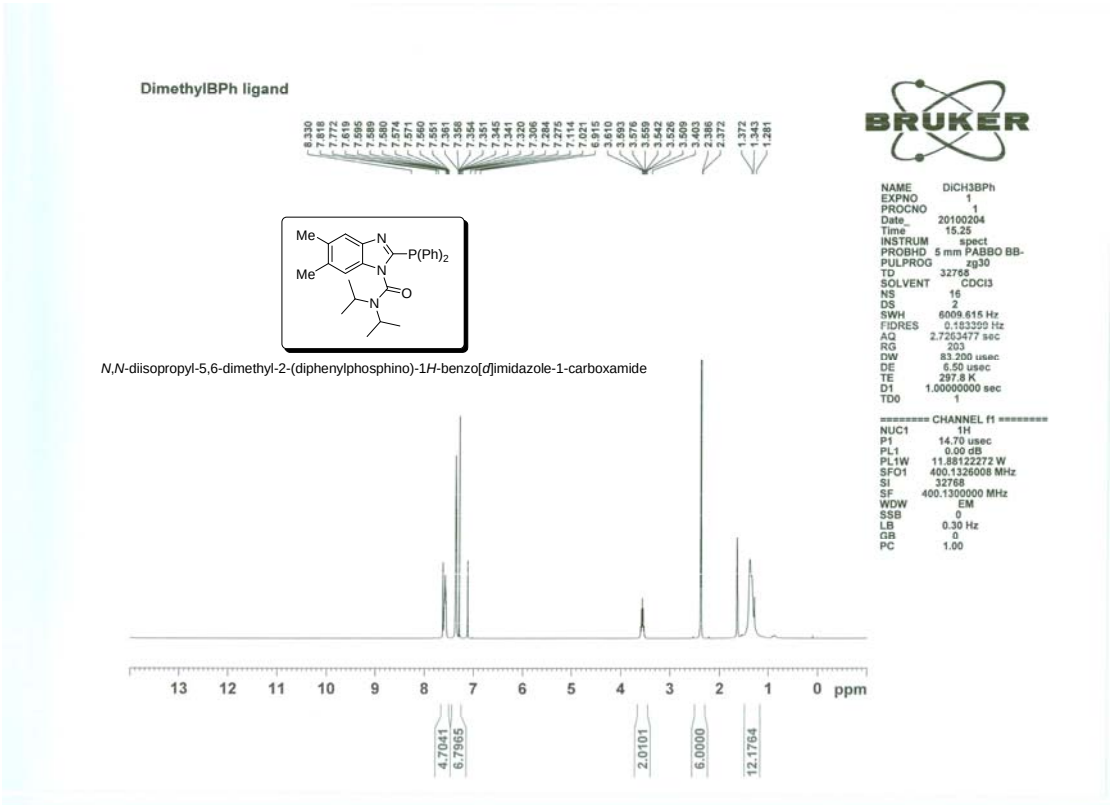
^{31}P NMR of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



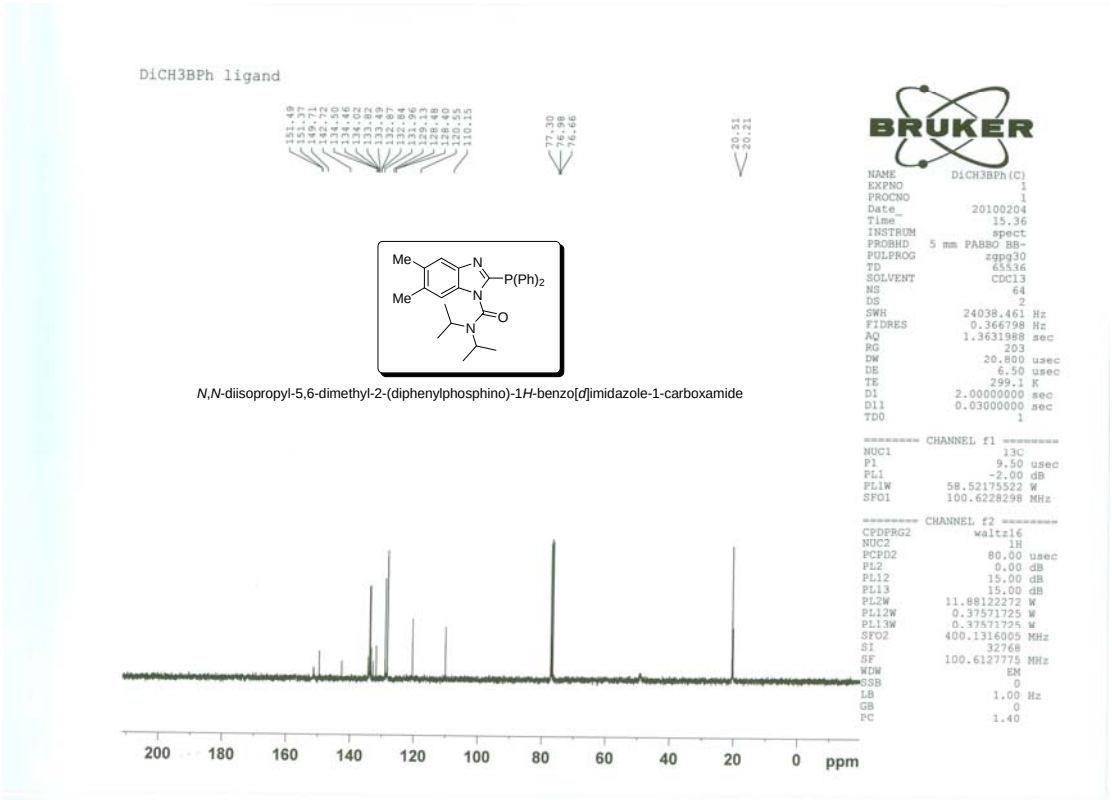
High resolution mass spectrum of 2-(di-tert-butylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



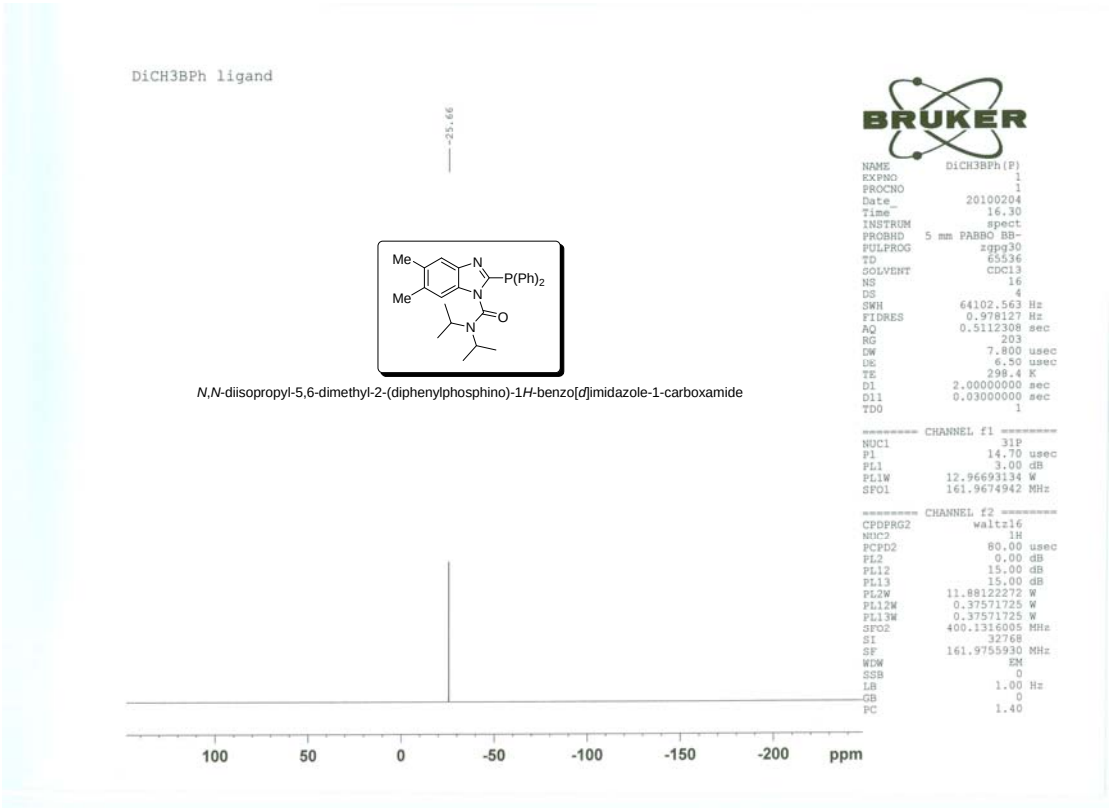
^{1}H NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



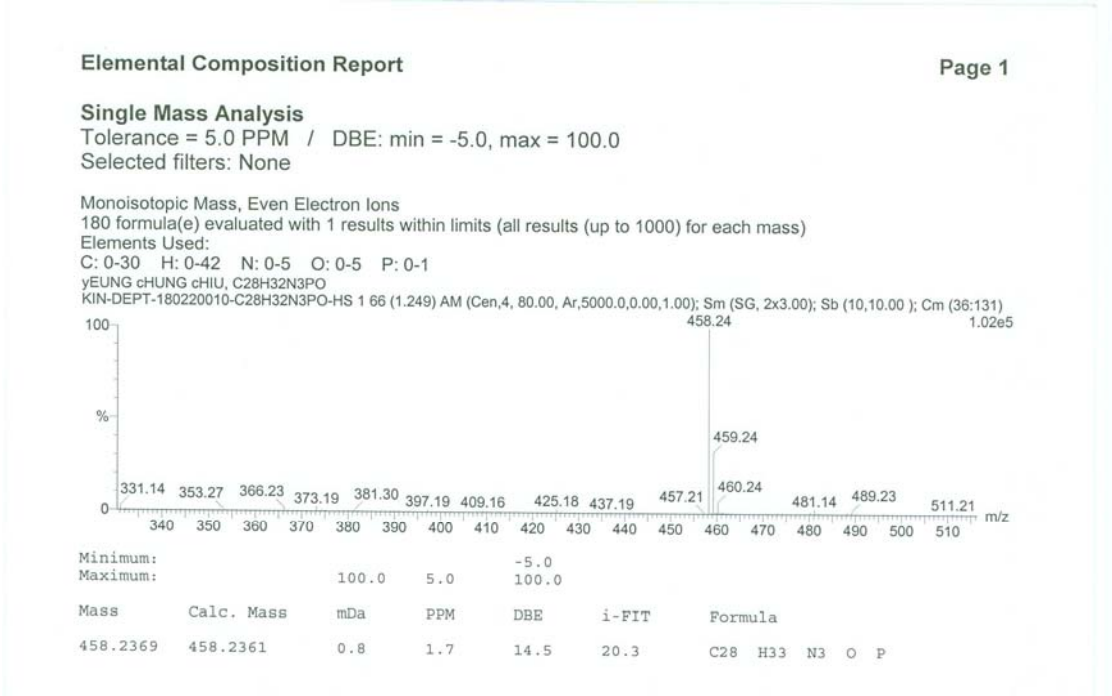
^{13}C NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



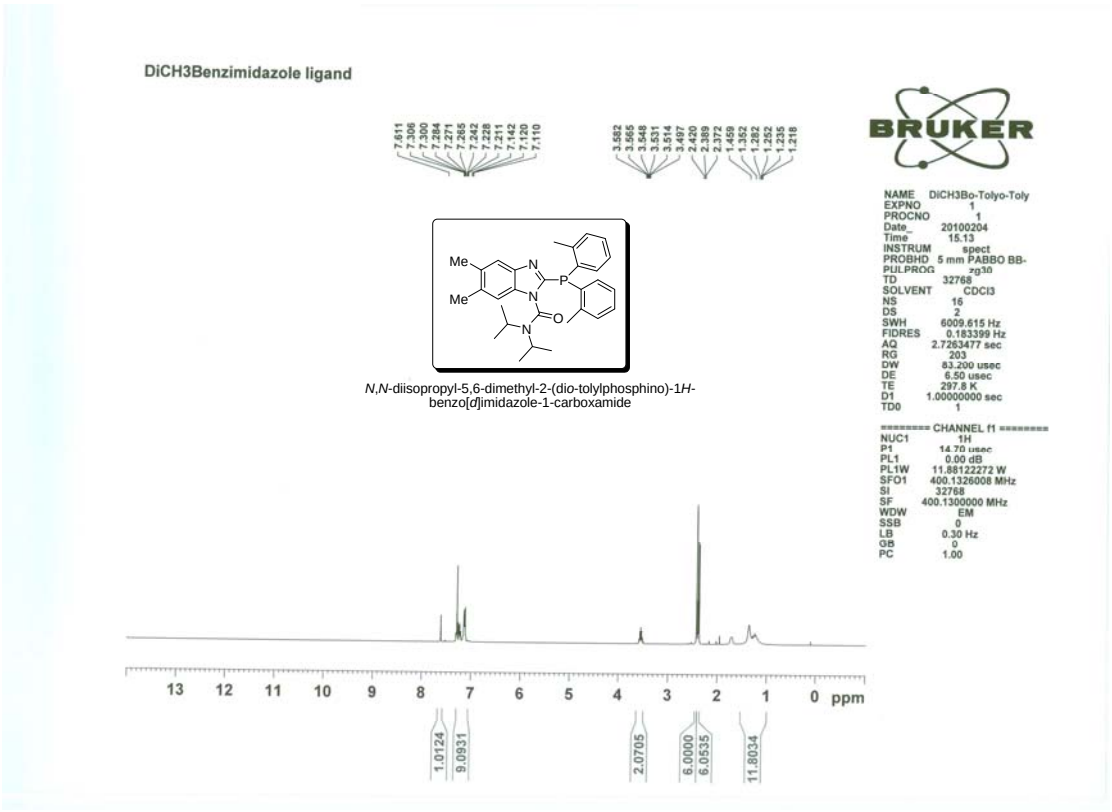
^{31}P NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



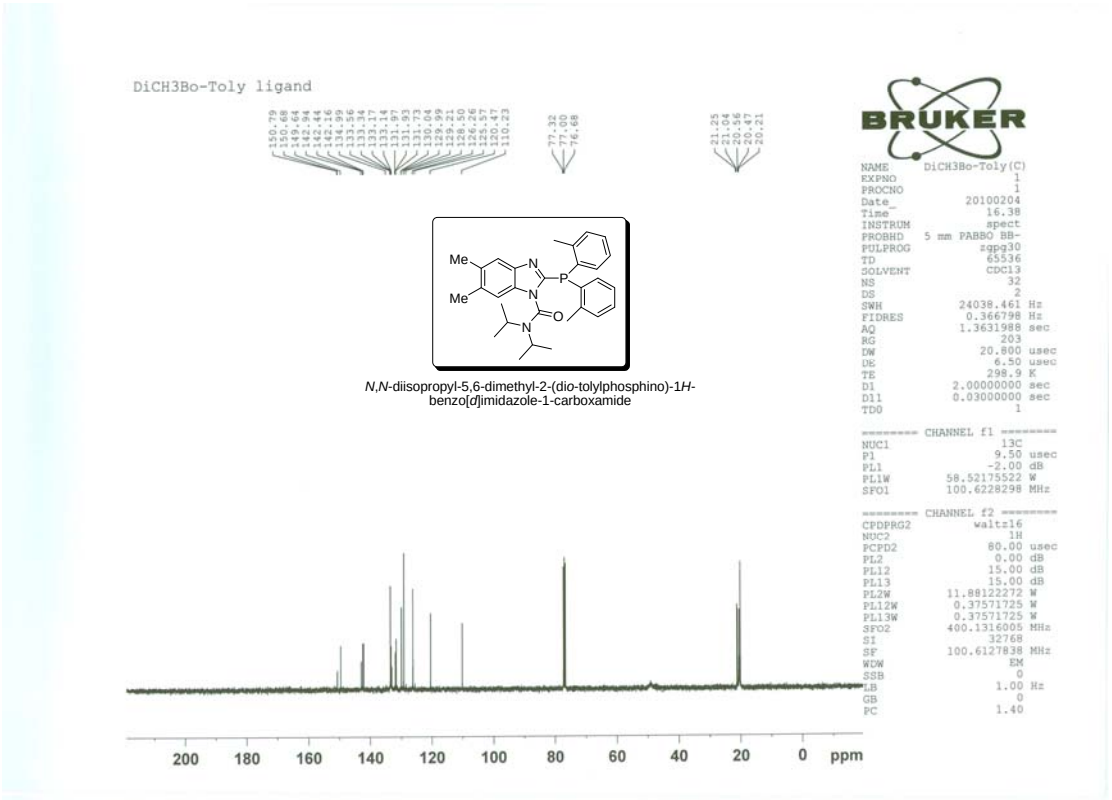
High resolution mass spectrum of *N*,*N*-diisopropyl-5,6-dimethyl-2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide



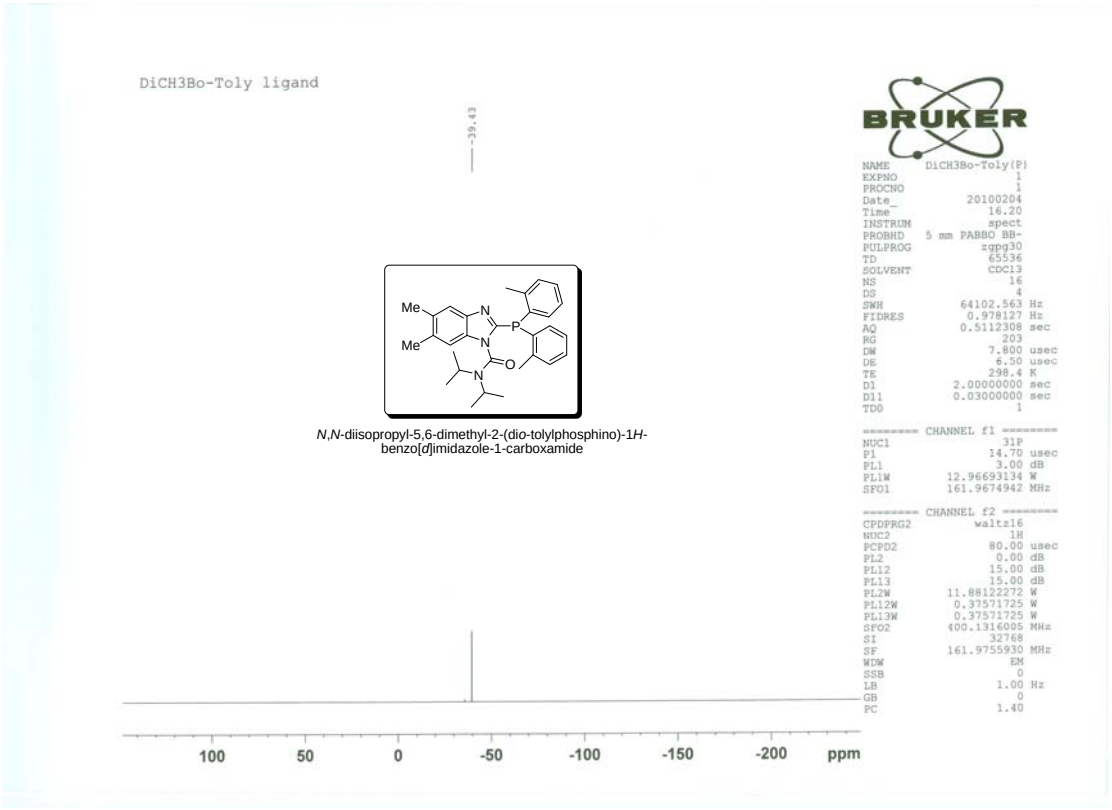
^{1}H NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-benzo[d]imidazole-1-carboxamide



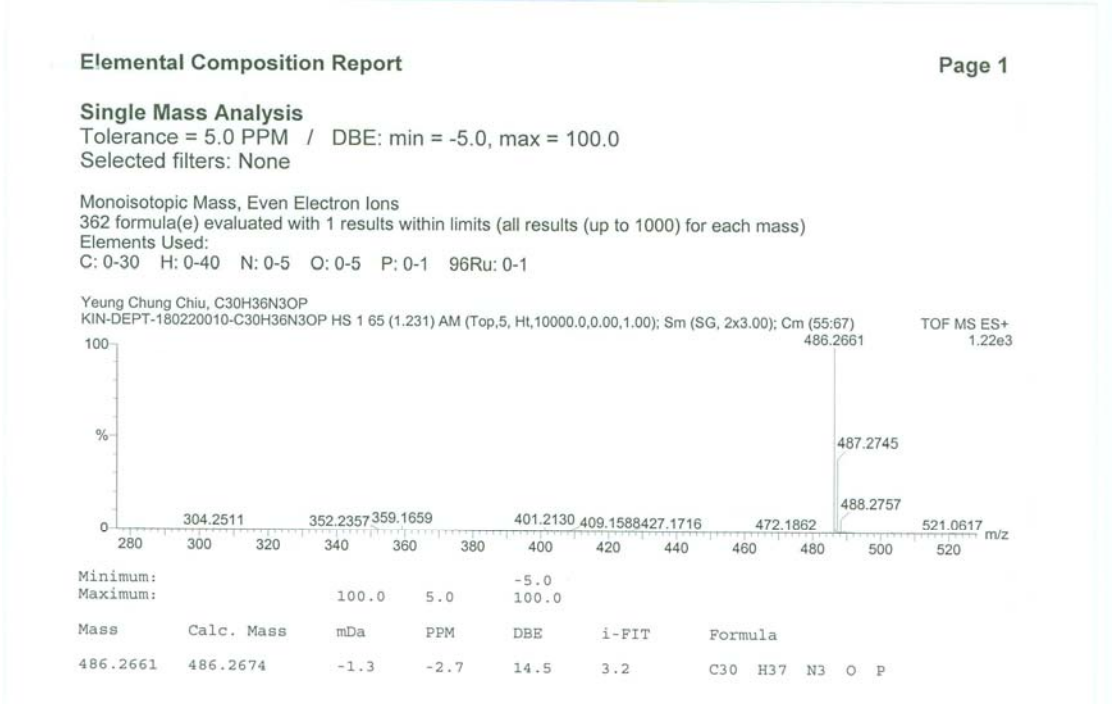
^{13}C NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-benzo[d]imidazole-1-carboxamide



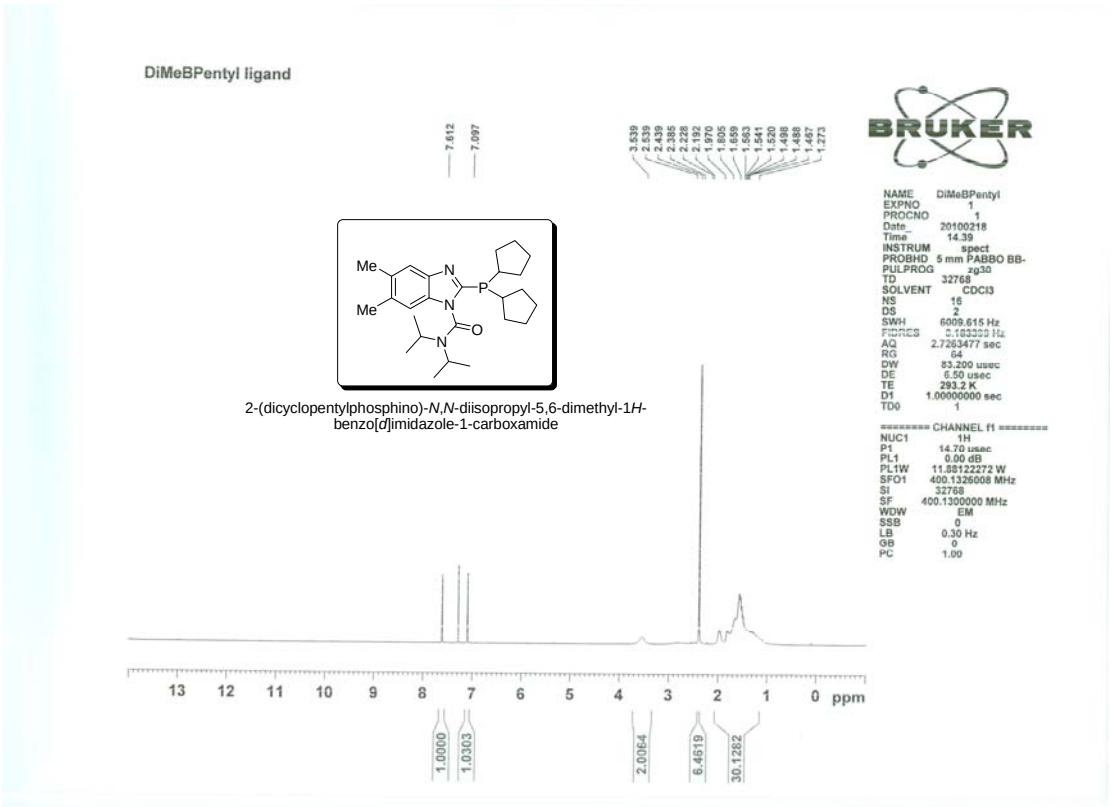
^{31}P NMR of *N*,*N*-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-benzo[d]imidazole-1-carboxamide



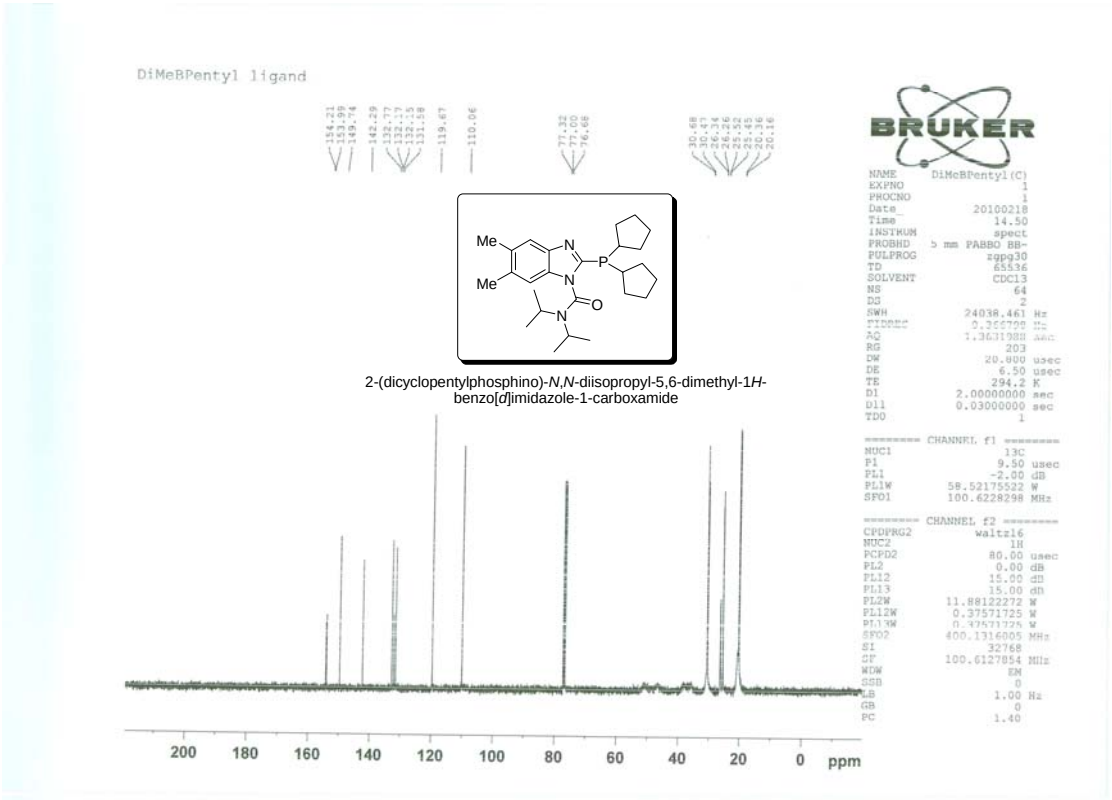
High resolution mass spectrum of *N*,*N*-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino)-1H-benzo[d]imidazole-1-carboxamide



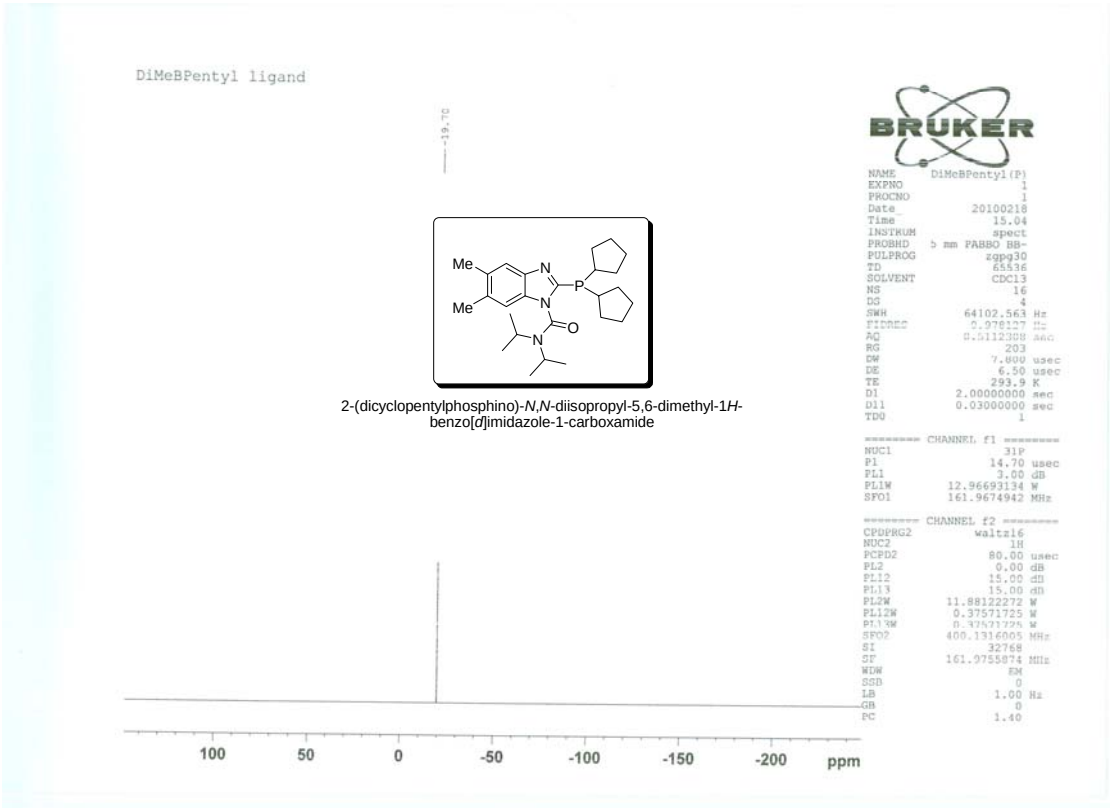
^{1}H NMR of 2-(dicyclopentylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



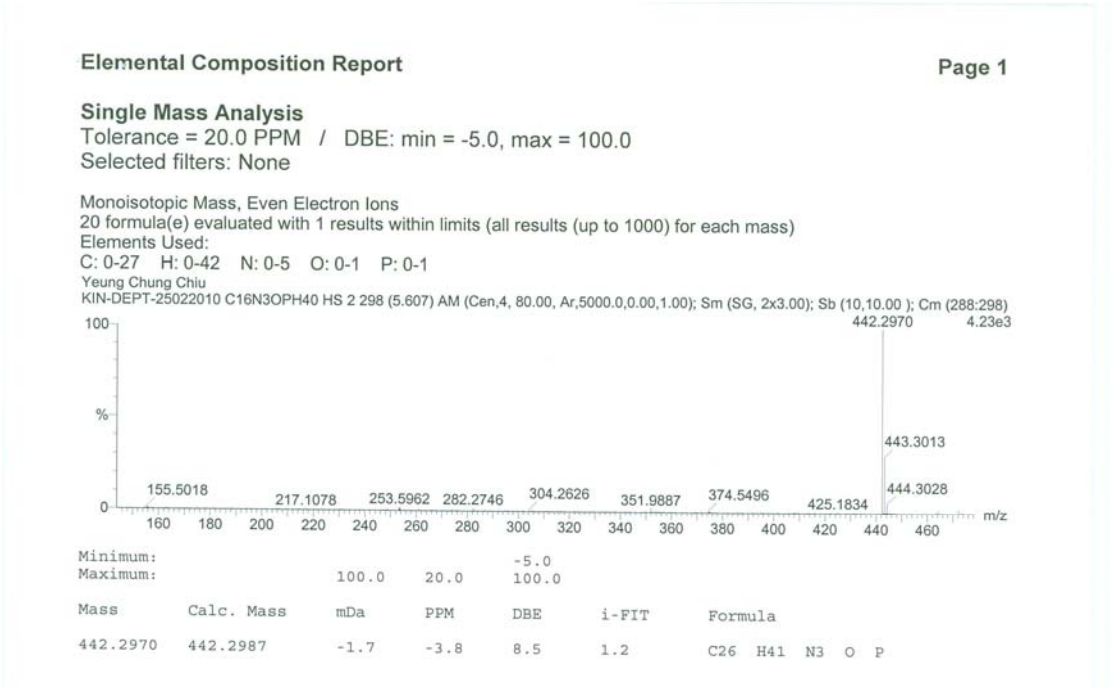
^{13}C NMR of 2-(dicyclopentylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



^{31}P NMR of 2-(dicyclopentylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide

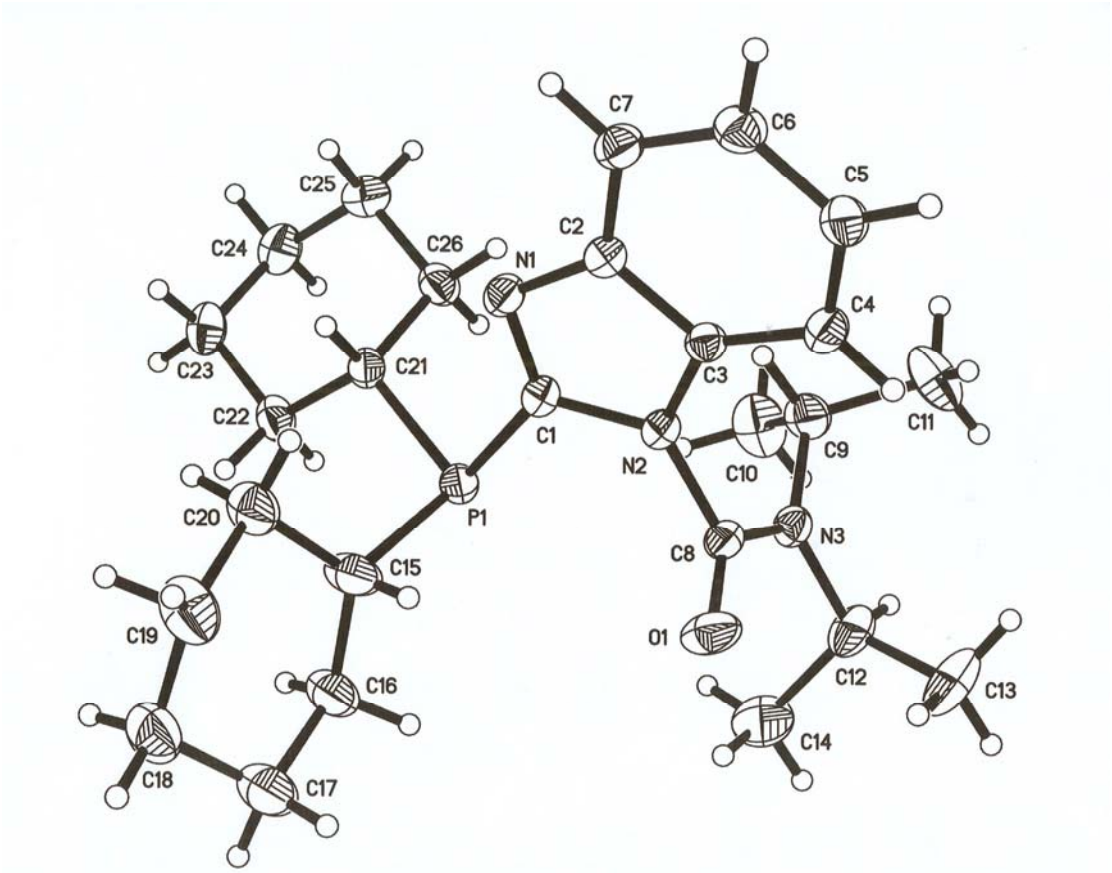


High resolution mass spectrum of 2-(dicyclopentylphosphino)-*N*,*N*-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



Chapter 3: X-Ray structure of ligands

X-Ray structure of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide



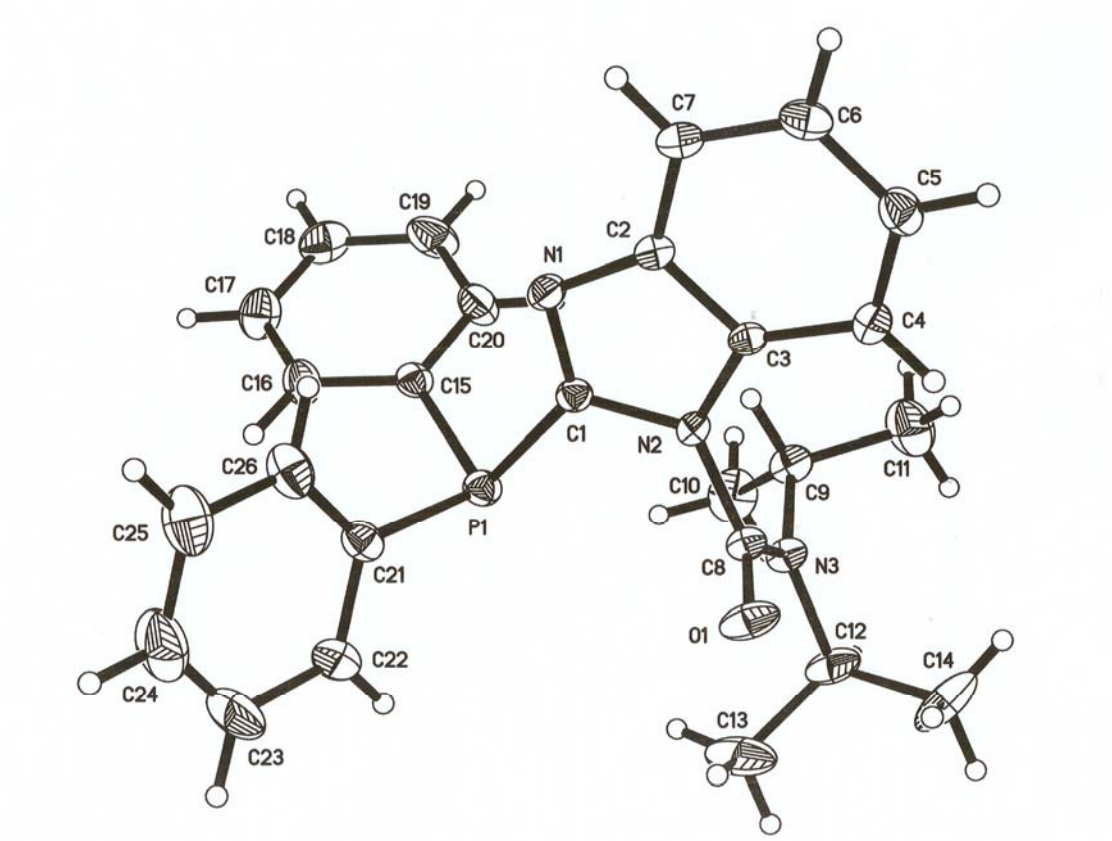
X-Ray data of 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-benzo[d]imidazole-1-carboxamide

Table 1. Crystal data and structure refinement for BCYCC26 (13 May 2010).

Identification code	ycc26	
Empirical formula	C_{26} H_{40} N_3 O P	
Formula weight	441.58	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.1446(2) Å	α= 90°.
	b = 15.3354(3) Å	β= 93.3020(10)°.
	c = 20.6322(4) Å	γ = 90°.
Volume	2572.70(9) $Å^3$	
Z	4	
Density (calculated)	1.140 Mg/m^3	
Absorption coefficient	0.128 mm^{-1}	
F(000)	960	
Crystal size	0.32 x 0.30 x 0.28 mm^3	
Theta range for data collection	1.66 to 27.35°.	
Index ranges	-10<=h<=10, -19<=k<=19, -25<=l<=26	
Reflections collected	31334	
Independent reflections	5790 [R(int) = 0.0654]	
Completeness to theta = 27.35°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9650 and 0.9601	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5790 / 12 / 316	
Goodness-of-fit on F^2	1.004	
Final R indices [I>2sigma(I)]	R1 = 0.0643, wR2 = 0.1751	
R indices (all data)	R1 = 0.1221, wR2 = 0.2092	
Largest diff. peak and hole	0.177 and -0.576 $e.Å^{-3}$	

1

X-Ray structure of N,N-diisopropyl 2-(diphenylphosphino)-
1H-benzo[d]imidazole-1-carboxamide



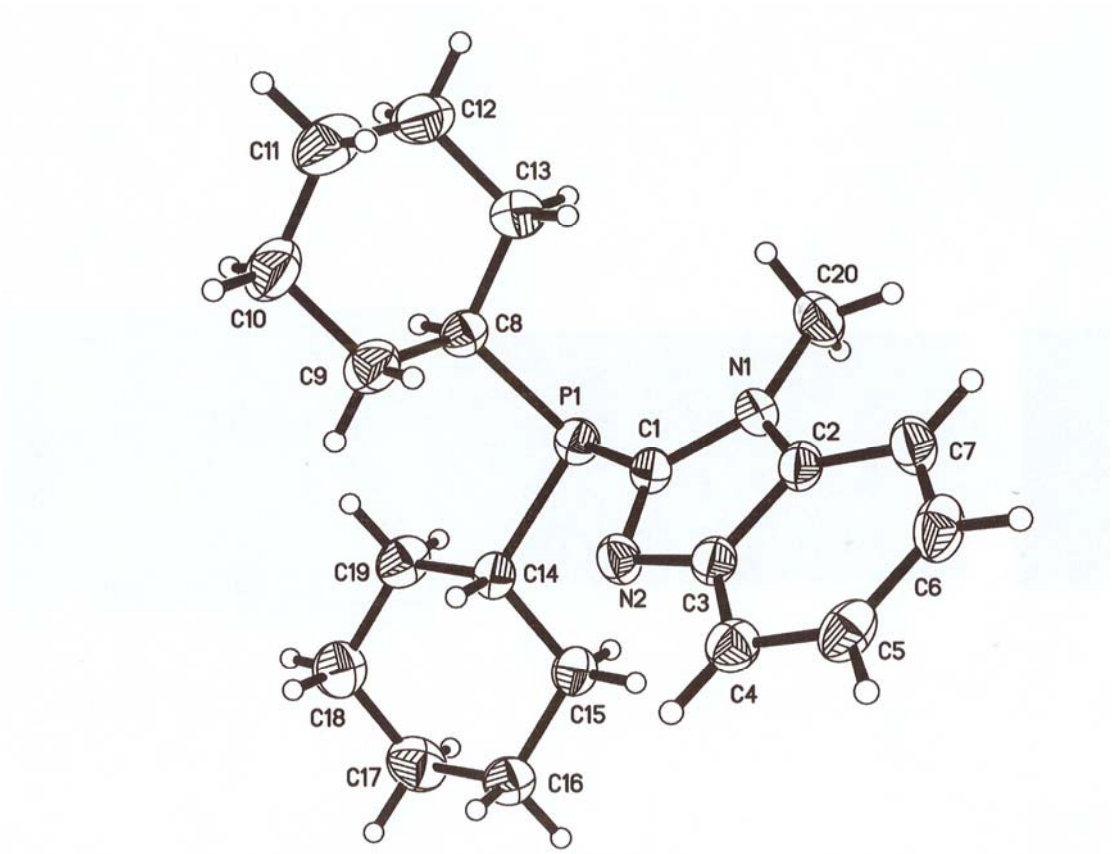
X-Ray data of N,N-diisopropyl 2-(diphenylphosphino)-1H-benzo[d]imidazole-1-carboxamide

Table 1. Crystal data and structure refinement for BCYCC32 (14 Jul 2010).

Identification code	ycc32	
Empirical formula	C_{26} H28 N_3 O P	
Formula weight	429.48	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.6184(2) Å	α= 90°.
	b = 15.6177(4) Å	β= 90°.
	c = 20.1914(7) Å	γ = 90°.
Volume	2402.41(12) $Å^3$	
Z	4	
Density (calculated)	1.187 Mg/m^3	
Absorption coefficient	0.136 mm^{-1}	
F(000)	912	
Crystal size	0.28 x 0.20 x 0.18 mm^3	
Theta range for data collection	2.02 to 27.35°.	
Index ranges	-9<=h<=9, -20<=k<=17, -26<=l<=17	
Reflections collected	17124	
Independent reflections	5369 [R(int) = 0.0626]	
Completeness to theta = 27.35°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9759 and 0.9629	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5369 / 0 / 280	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2sigma(I)]	R1 = 0.0560, wR2 = 0.1103	
R indices (all data)	R1 = 0.1162, wR2 = 0.1303	
Absolute structure parameter	-0.13(13)	
Largest diff. peak and hole	0.533 and -0.200 $e.Å^{-3}$	

1

X-Ray structure of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole



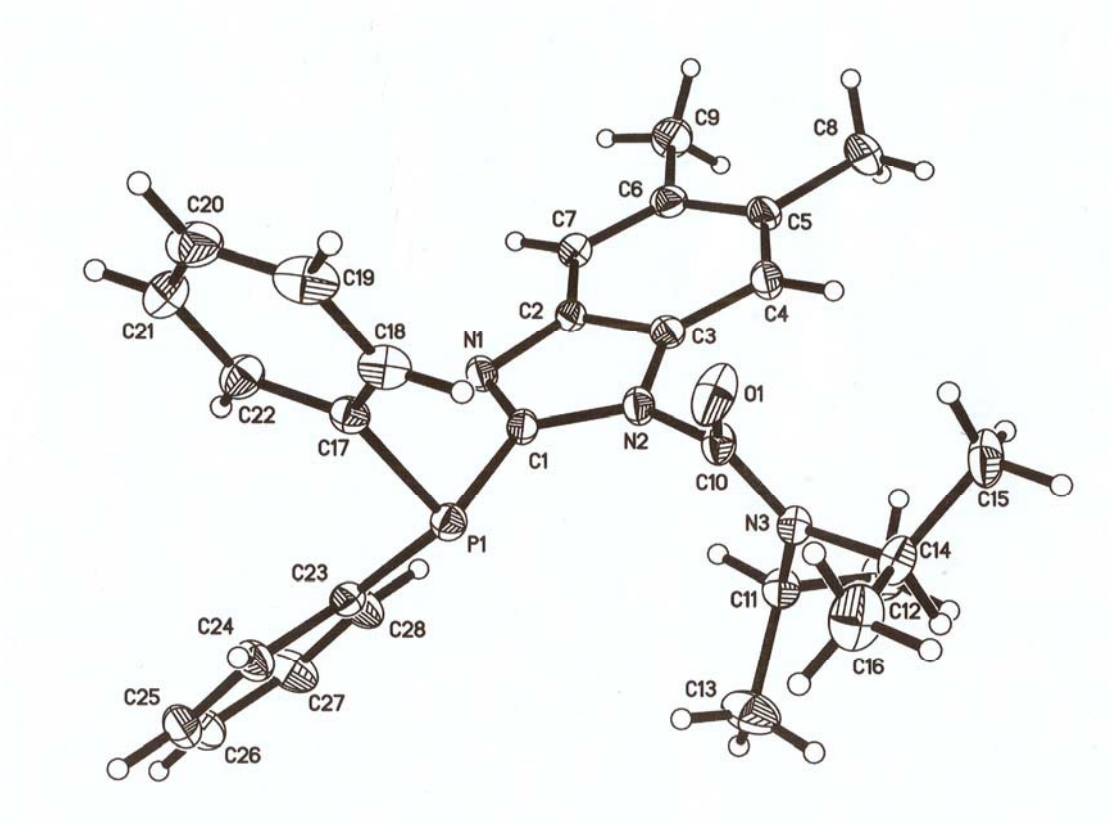
X-Ray data of 2-(dicyclohexylphosphino)-1-methyl-1H-benzo[d]imidazole

Table 1. Crystal data and structure refinement for BCYCC33 (26 Jul 2010).

Identification code	ycc33	
Empirical formula	C_{20} H_{29} N_2 P	
Formula weight	328.42	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 10.5931(3) Å	α= 90°.
	b = 10.3544(3) Å	β= 90°.
	c = 34.0185(11) Å	γ = 90°.
Volume	3731.33(19) $Å^3$	
Z	8	
Density (calculated)	1.169 Mg/m^3	
Absorption coefficient	0.150 mm^{-1}	
F(000)	1424	
Crystal size	0.38 x 0.38 x 0.38 mm^3	
Theta range for data collection	2.26 to 27.36°.	
Index ranges	-13<=h<=11, -12<=k<=13, -43<=l<=26	
Reflections collected	23907	
Independent reflections	4205 [R(int) = 0.0959]	
Completeness to theta = 27.36°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9454 and 0.9454	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4205 / 0 / 208	
Goodness-of-fit on F^2	1.004	
Final R indices [I>2sigma(I)]	R1 = 0.0629, wR2 = 0.1537	
R indices (all data)	R1 = 0.1468, wR2 = 0.1870	
Largest diff. peak and hole	0.328 and -0.236 $e.Å^{-3}$	

1

X-Ray structure of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide



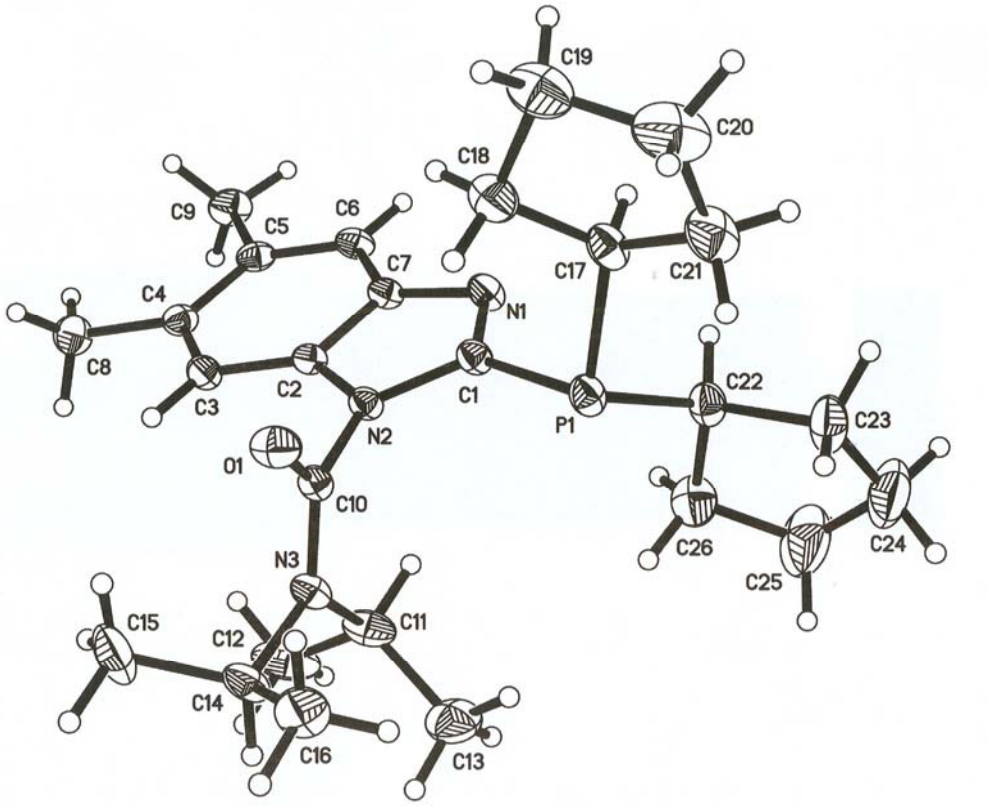
X-Ray data of 2-(dicyclohexylphosphino)-N,N-diisopropyl-5,6-dimethyl-1H-benzo[d]imidazole-1-carboxamide

Table 1. Crystal data and structure refinement for BCYCC22 (31 Mar 2010).

Identification code	ycc22	
Empirical formula	C_{28} H_{32} N_3 O P	
Formula weight	457.54	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.81540(10) Å	α= 90°.
	b = 12.6075(2) Å	β= 97.3000(10)°.
	c = 13.0798(2) Å	γ = 90°.
Volume	1278.34(3) Å^3	
Z	2	
Density (calculated)	1.189 Mg/m^3	
Absorption coefficient	0.132 mm^{-1}	
F(000)	488	
Crystal size	0.50 x 0.50 x 0.48 mm^3	
Theta range for data collection	2.25 to 27.45°.	
Index ranges	-10<=h<=10, -16<=k<=16, -16<=l<=16	
Reflections collected	13582	
Independent reflections	5451 [R(int) = 0.0340]	
Completeness to theta = 27.45°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.743	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5451 / 1 / 298	
Goodness-of-fit on F^2	1.002	
Final R indices [I>2sigma(I)]	R1 = 0.0414, wR2 = 0.0949	
R indices (all data)	R1 = 0.0590, wR2 = 0.1041	
Absolute structure parameter	-0.12(8)	
Largest diff. peak and hole	0.176 and -0.191 e.Å^{-3}	

1

X-Ray structure of 2-(dicyclopentylphosphino)-N,N-diisopropyl-5,6-dimethyl -1H-benzo[d]imidazole-1-carboxamide



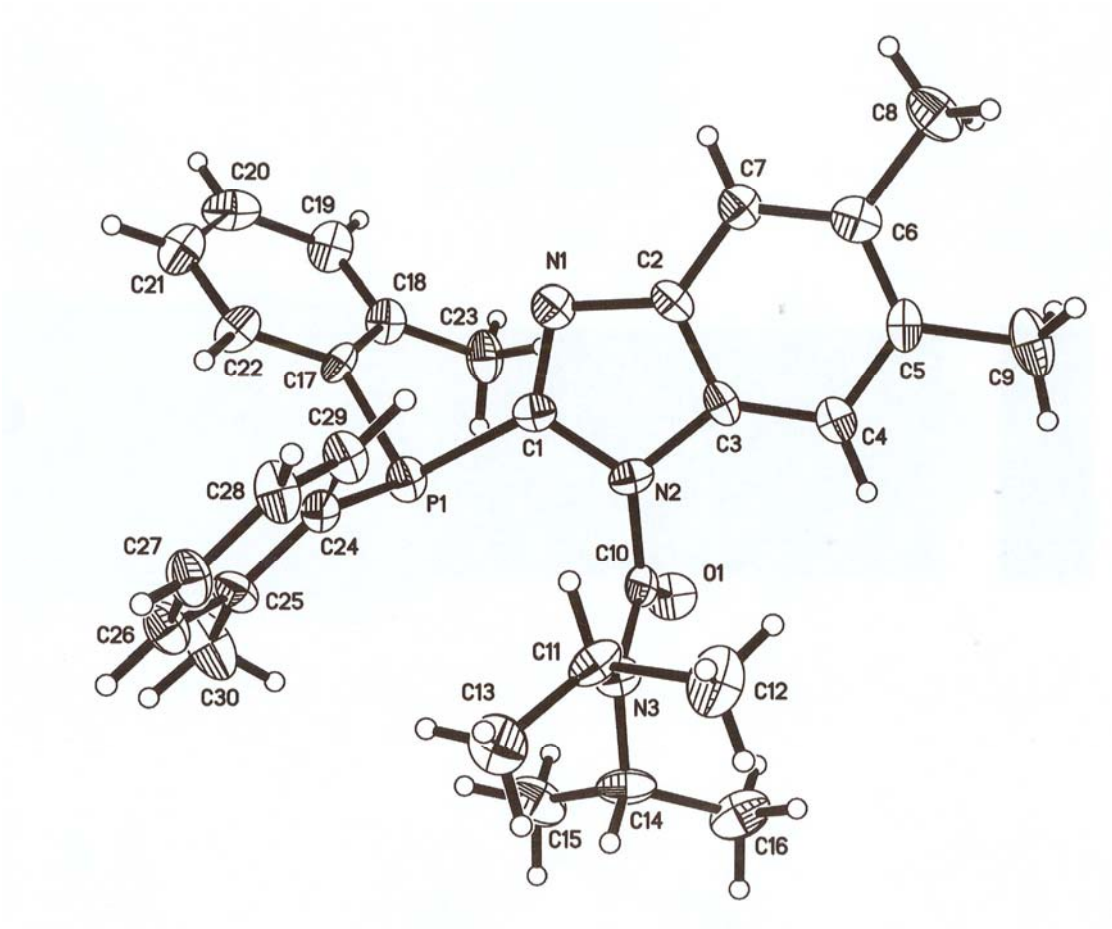
X-Ray data of 2-(dicyclopentylphosphino)-N,N-diisopropyl-5,6-dimethyl -1H-benzo[d]imidazole-1-carboxamide

Table 1. Crystal data and structure refinement for BCYCC29 (7 Jul 2010).

Identification code	ycc29	
Empirical formula	C_{26} H_{40} N_3 O P	
Formula weight	441.58	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.3784(2) Å	α= 95.0800(10)°.
	b = 10.9102(2) Å	β= 92.0230(10)°.
	c = 13.9297(3) Å	γ = 113.6220(10)°.
Volume	1296.82(5) $Å^3$	
Z	2	
Density (calculated)	1.131 Mg/m^3	
Absorption coefficient	0.127 mm^{-1}	
F(000)	480	
Crystal size	0.36 x 0.30 x 0.26 mm^3	
Theta range for data collection	2.05 to 27.65°.	
Index ranges	-12<=h<=12, -14<=k<=14, -18<=l<=18	
Reflections collected	23378	
Independent reflections	5951 [R(int) = 0.0480]	
Completeness to theta = 27.65°	98.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.785	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5951 / 0 / 280	
Goodness-of-fit on F^2	1.006	
Final R indices [I>2sigma(I)]	R1 = 0.0575, wR2 = 0.1704	
R indices (all data)	R1 = 0.0941, wR2 = 0.1990	
Largest diff. peak and hole	0.305 and -0.270 $e.Å^{-3}$	

1

X-Ray structure of N,N-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino) 1H-benzo[d]imidazole-1-carboxamide



X-Ray data of N,N-diisopropyl-5,6-dimethyl-2-(dio-tolylphosphino) 1H-benzo[d]imidazole-1-carboxamide

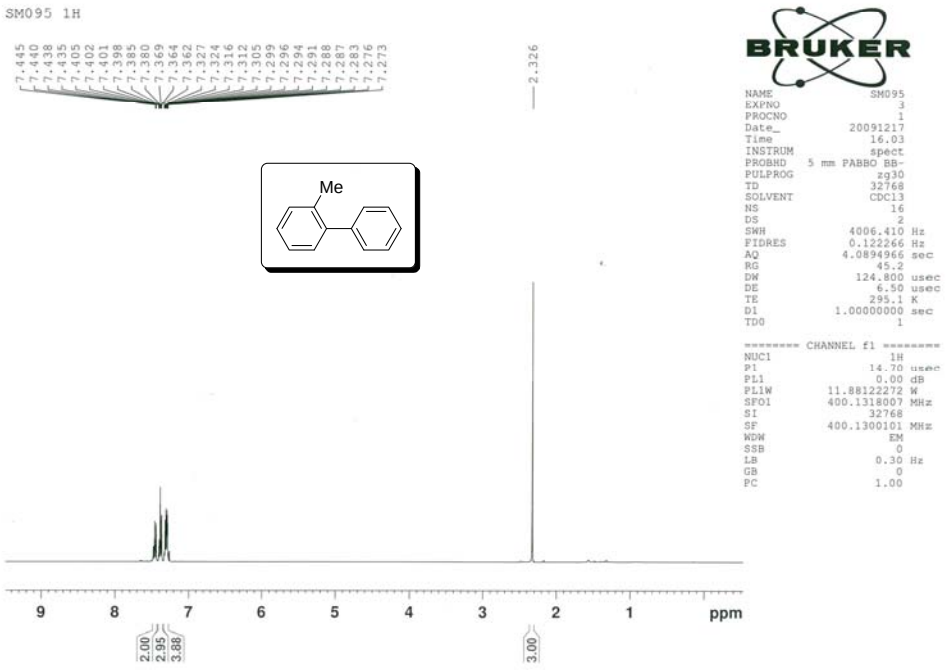
Table 1. Crystal data and structure refinement for BCYCC31 (13 Jul 2010).

Identification code	ycc31	
Empirical formula	C_{30} H_{36} N_3 O P	
Formula weight	485.59	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.5998(13) Å	α= 90°.
	b = 18.648(3) Å	β= 93.172(8)°.
	c = 19.143(3) Å	γ = 90°.
Volume	2708.9(8) $Å^3$	
Z	4	
Density (calculated)	1.191 Mg/m^3	
Absorption coefficient	0.128 mm^{-1}	
F(000)	1040	
Crystal size	0.26 x 0.10 x 0.06 mm^3	
Theta range for data collection	1.53 to 27.09°.	
Index ranges	-9<=h<=9, -23<=k<=23, -22<=l<=24	
Reflections collected	35476	
Independent reflections	5947 [R(int) = 0.6713]	
Completeness to theta = 27.09°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9923 and 0.9674	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5947 / 0 / 316	
Goodness-of-fit on F^2	0.929	
Final R indices [I>2sigma(I)]	R1 = 0.0841, wR2 = 0.0977	
R indices (all data)	R1 = 0.3264, wR2 = 0.1248	
Largest diff. peak and hole	0.237 and -0.311 $e.Å^{-3}$	

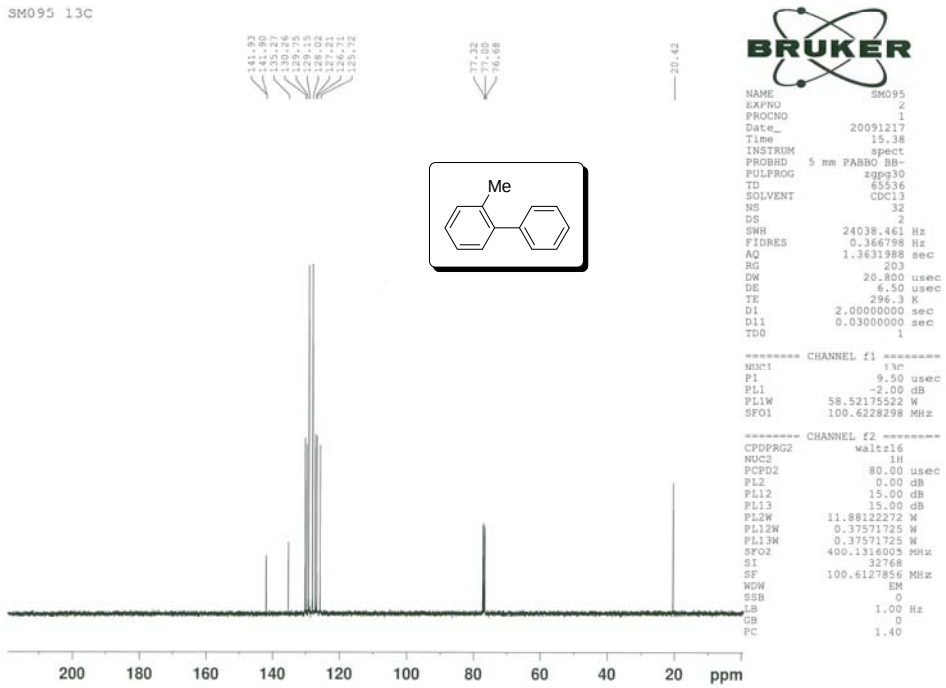
1

Chapter 3: NMR spectrum of cross-coupling products

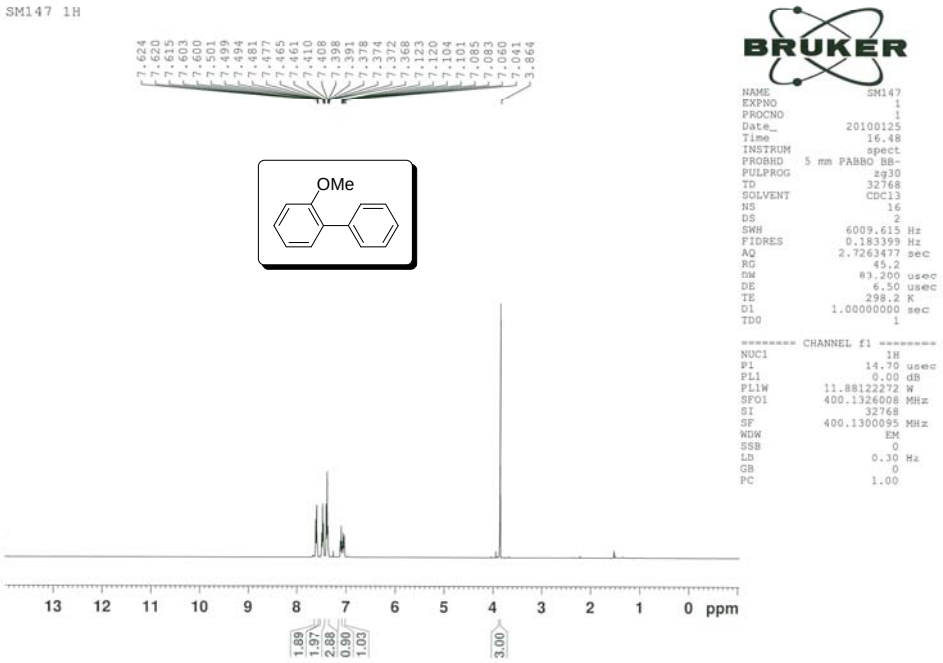
^{1}H NMR of entry 1 and 2



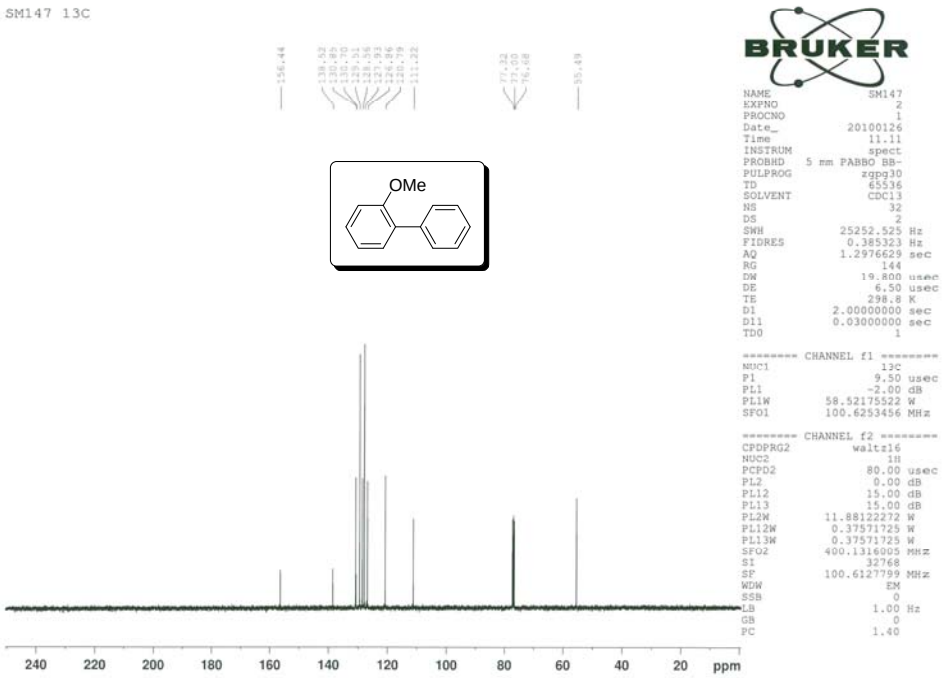
^{13}C NMR of entry 1 and 2



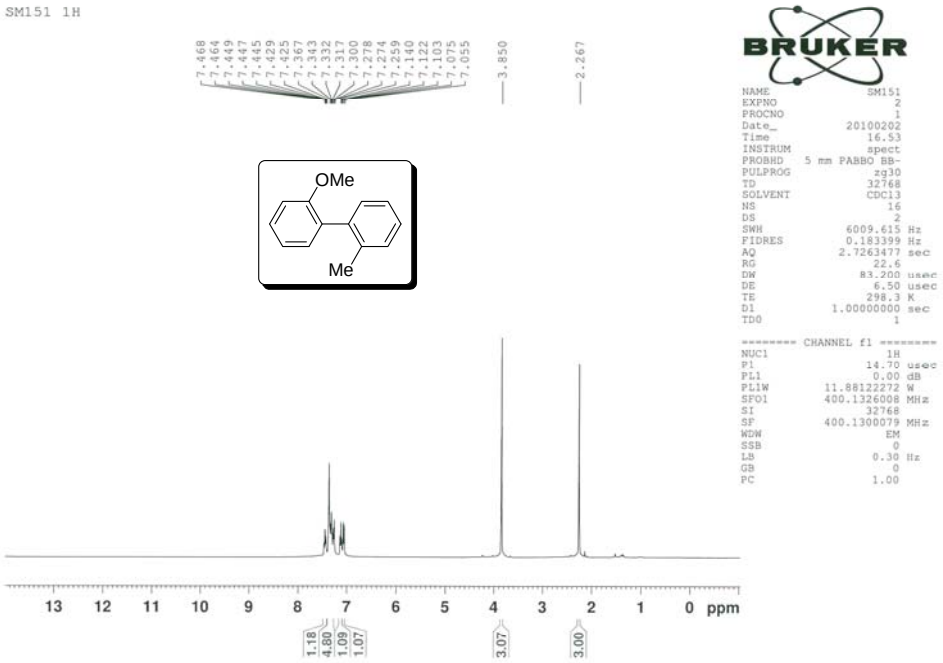
^{1}H NMR of entry 3



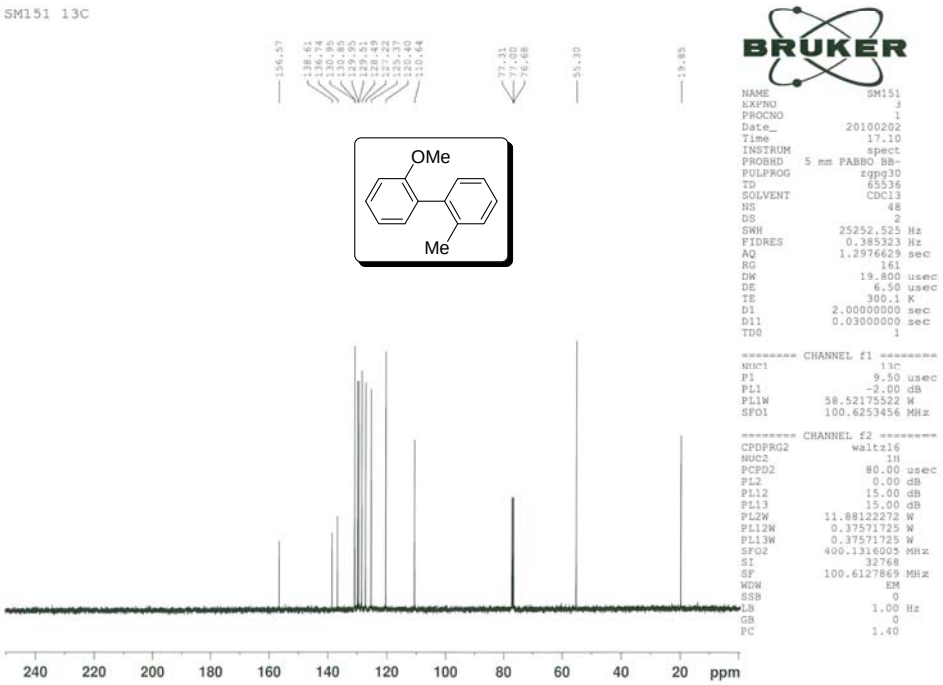
^{13}C NMR of entry 3



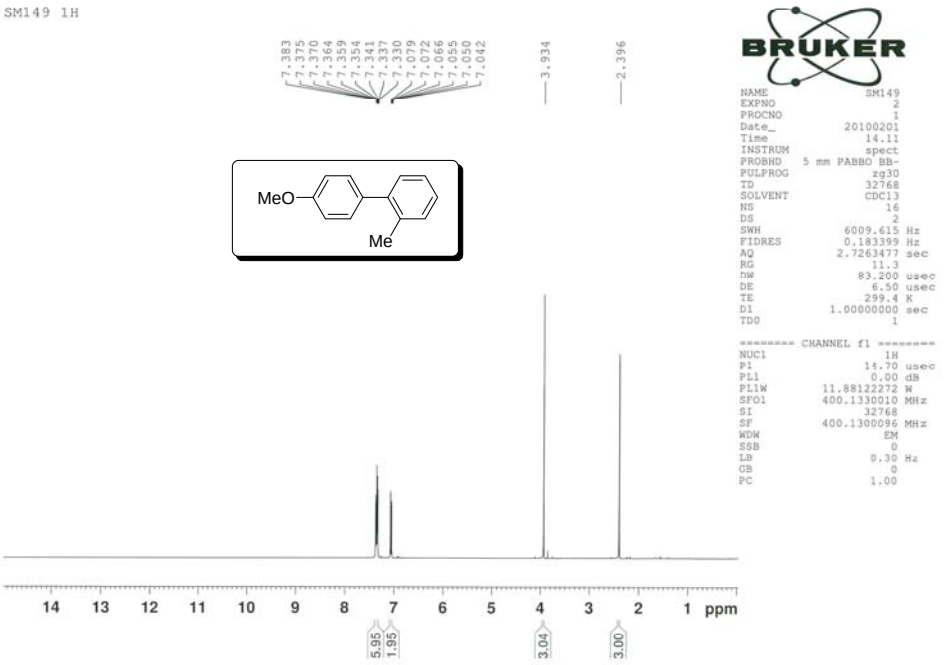
^{1}H NMR of entry 4



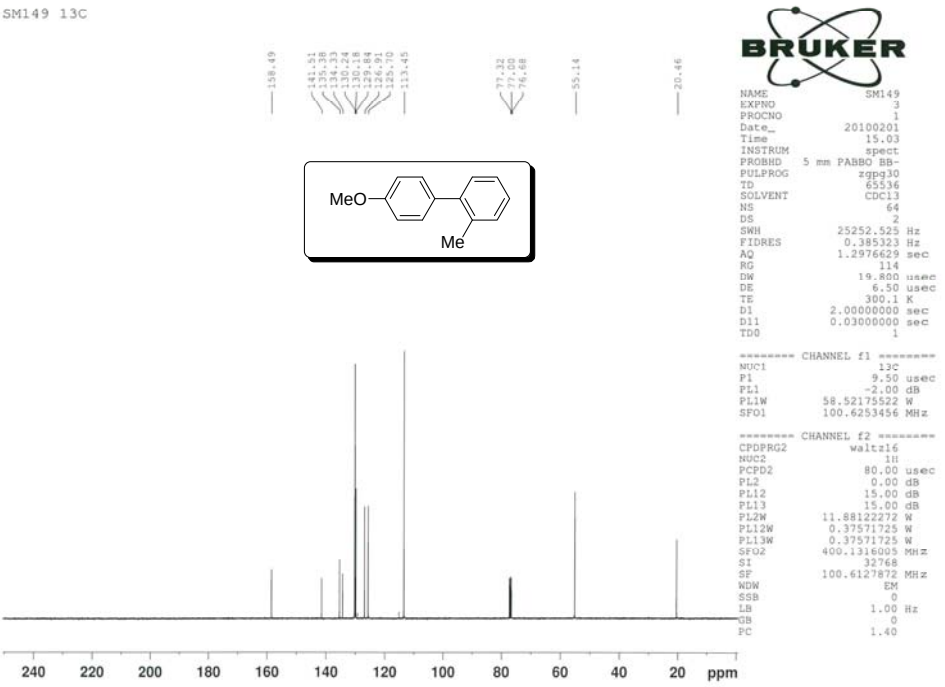
^{13}C NMR of entry 4



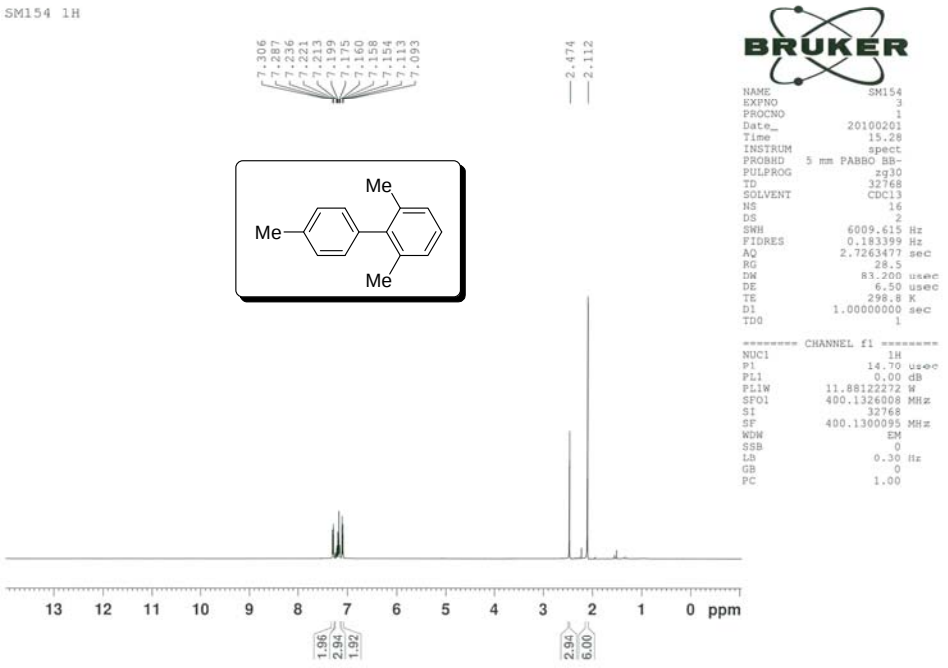
^{1}H NMR of entry 5



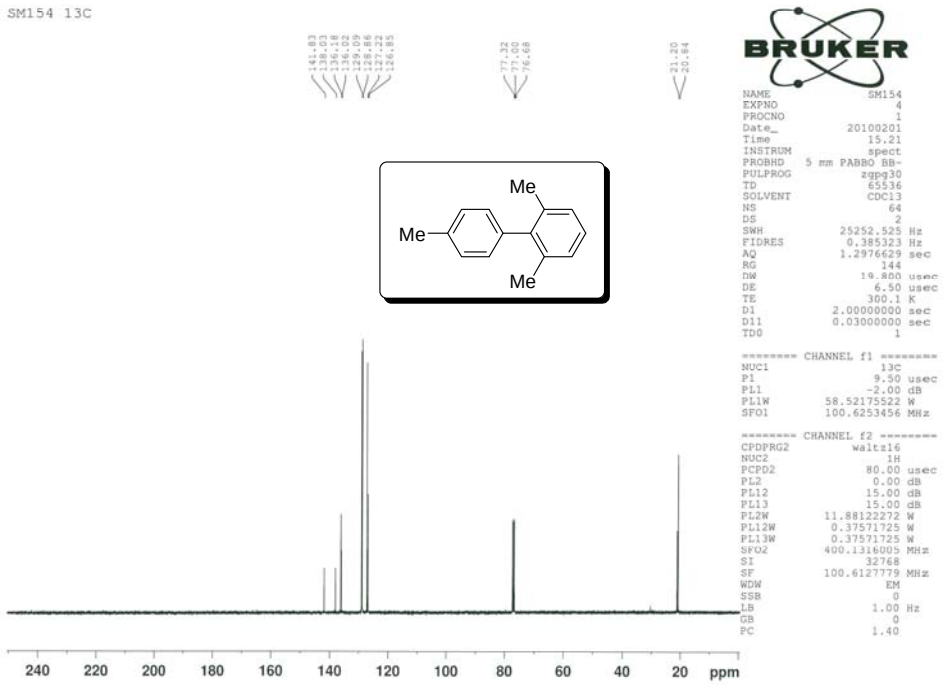
^{13}C NMR of entry 5



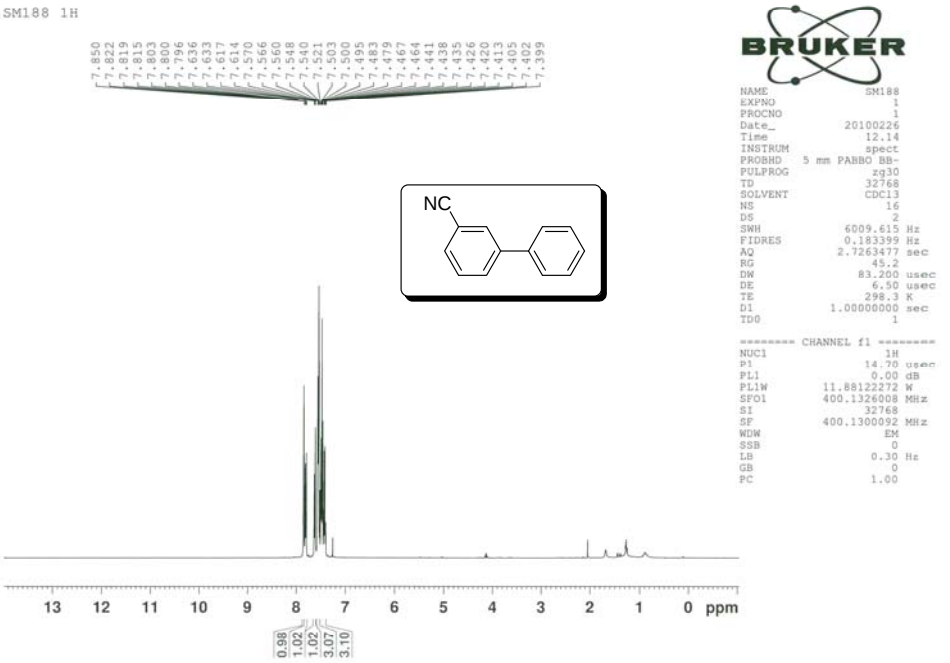
^{1}H NMR of entry 6



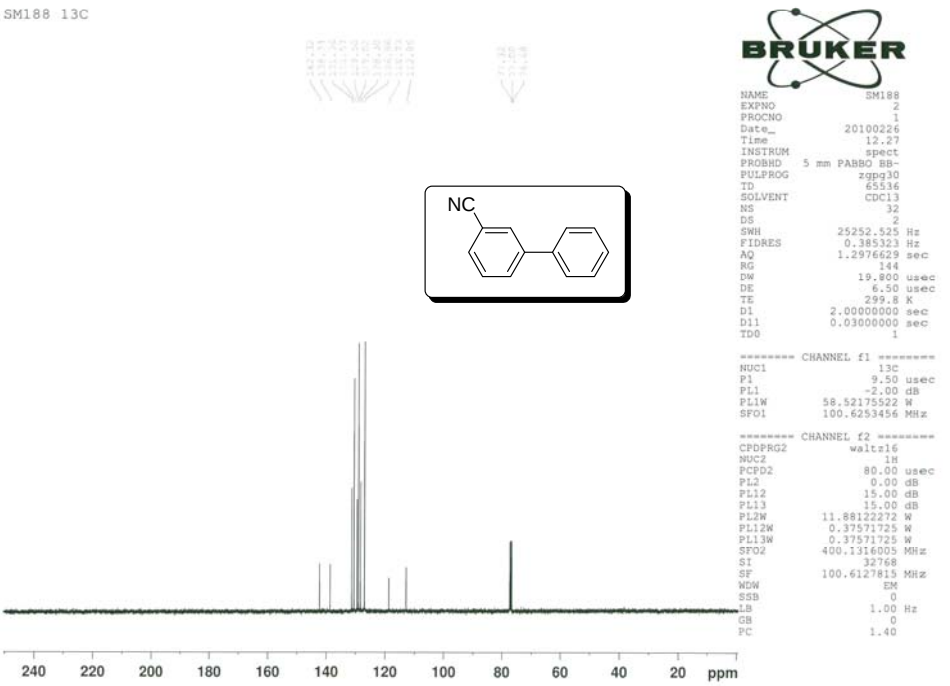
^{13}C NMR of entry 6



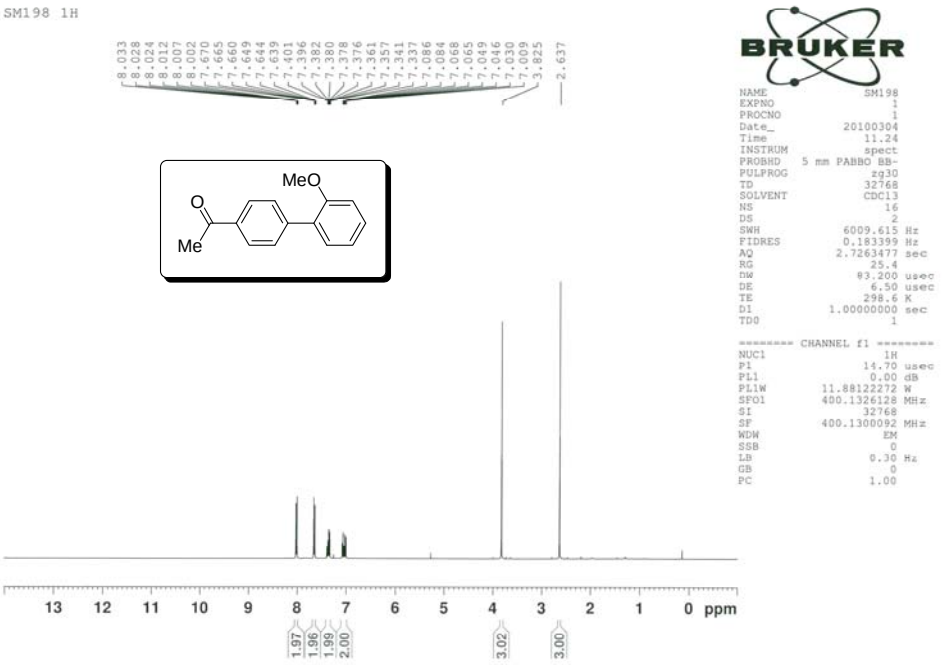
^{1}H NMR of entry 7



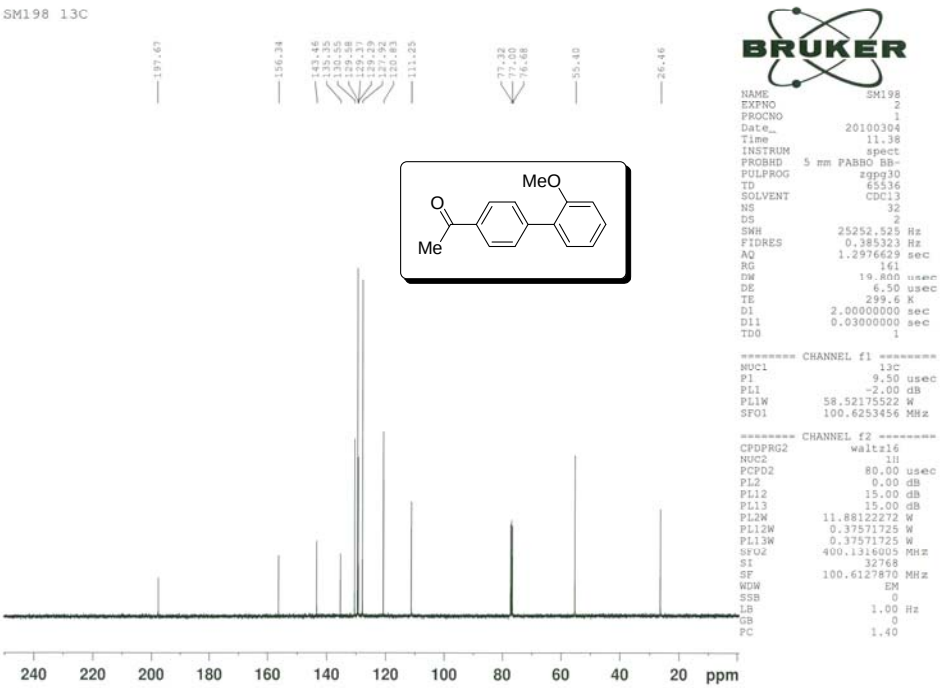
^{13}C NMR of entry 7



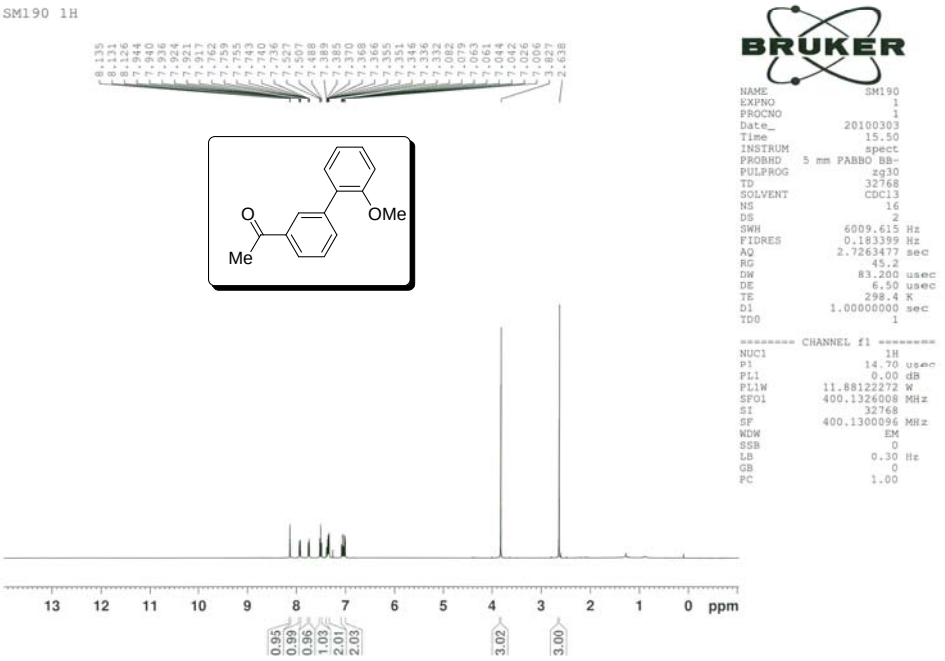
^{1}H NMR of entry 8



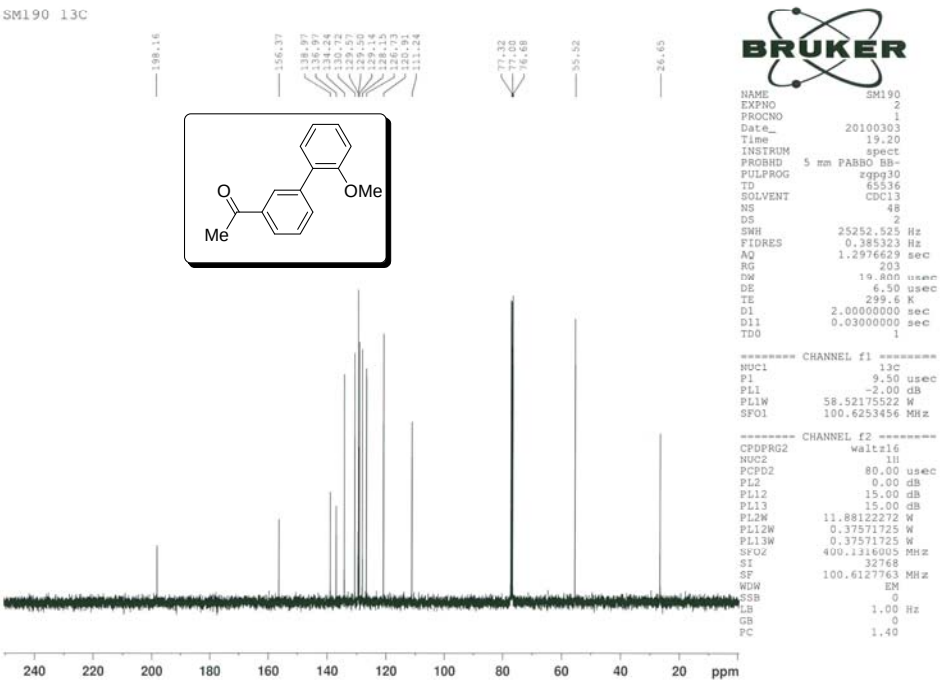
^{13}C NMR of entry 8



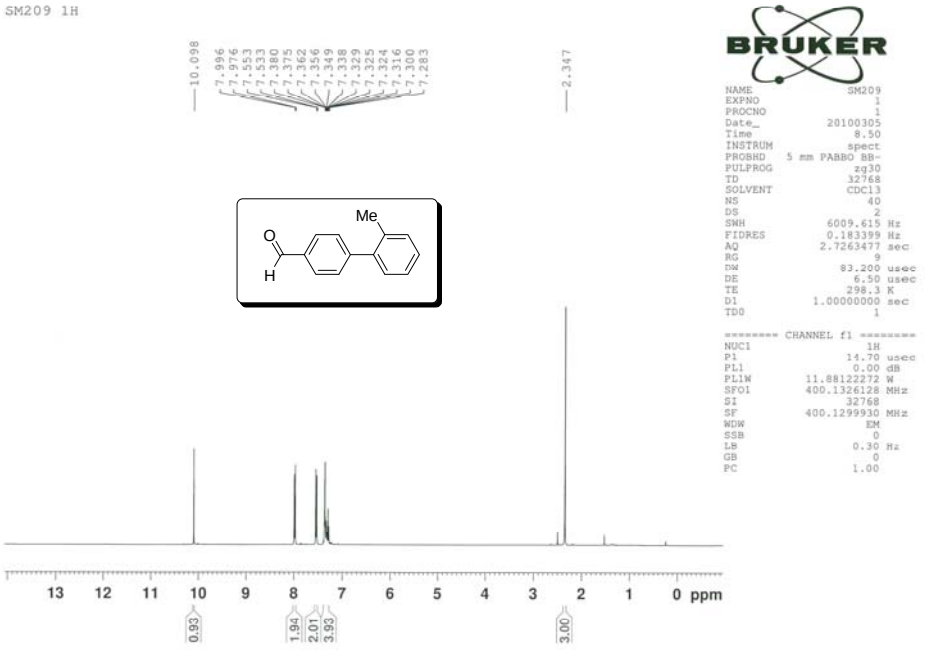
^{1}H NMR of entry 9



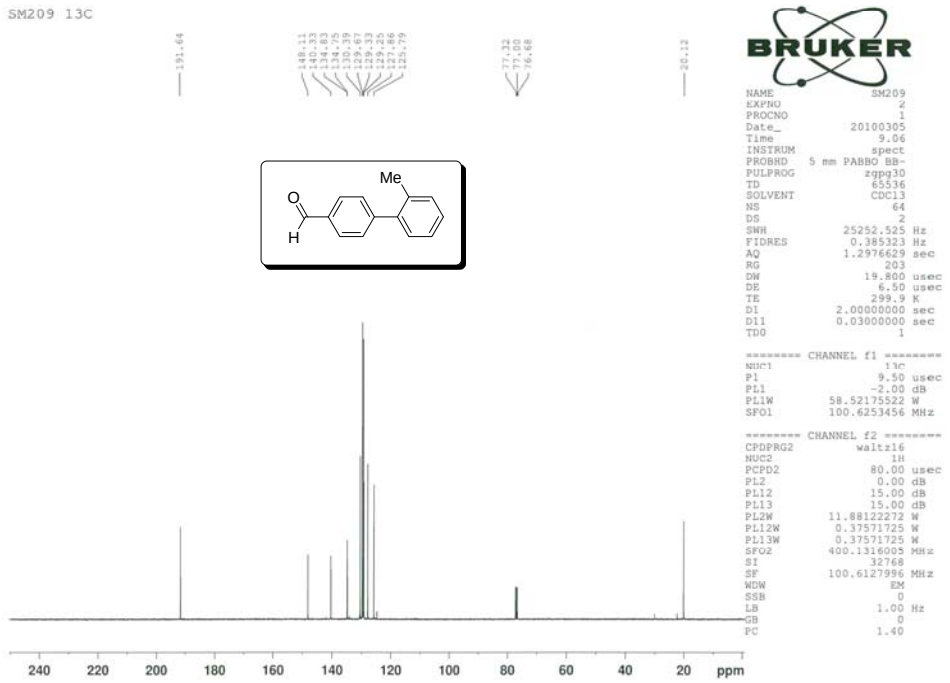
^{13}C NMR of entry 9



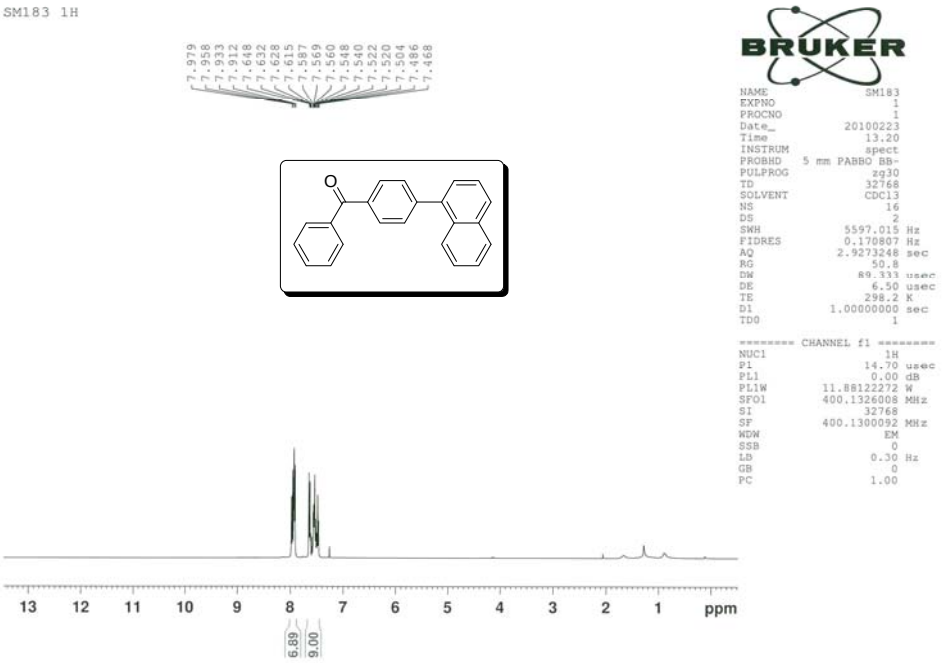
^{1}H NMR of entry 10



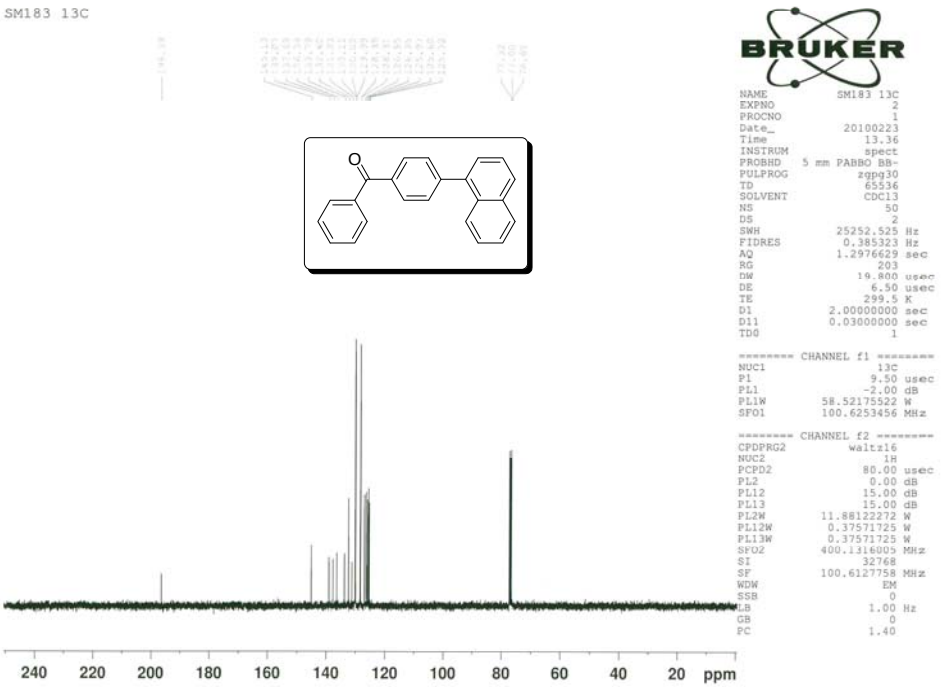
^{13}C NMR of entry 10



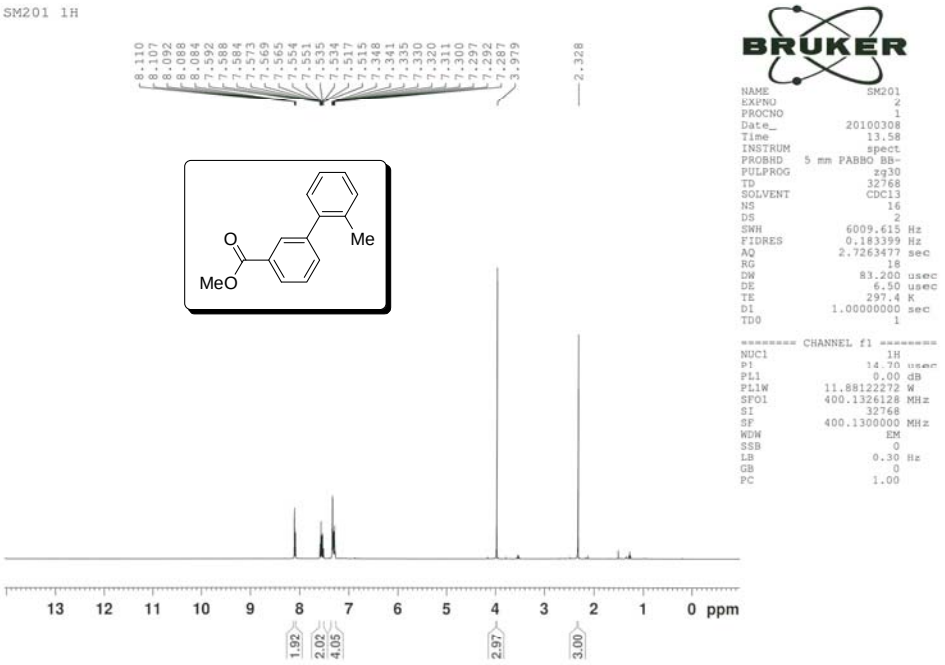
^{1}H NMR of entry 11



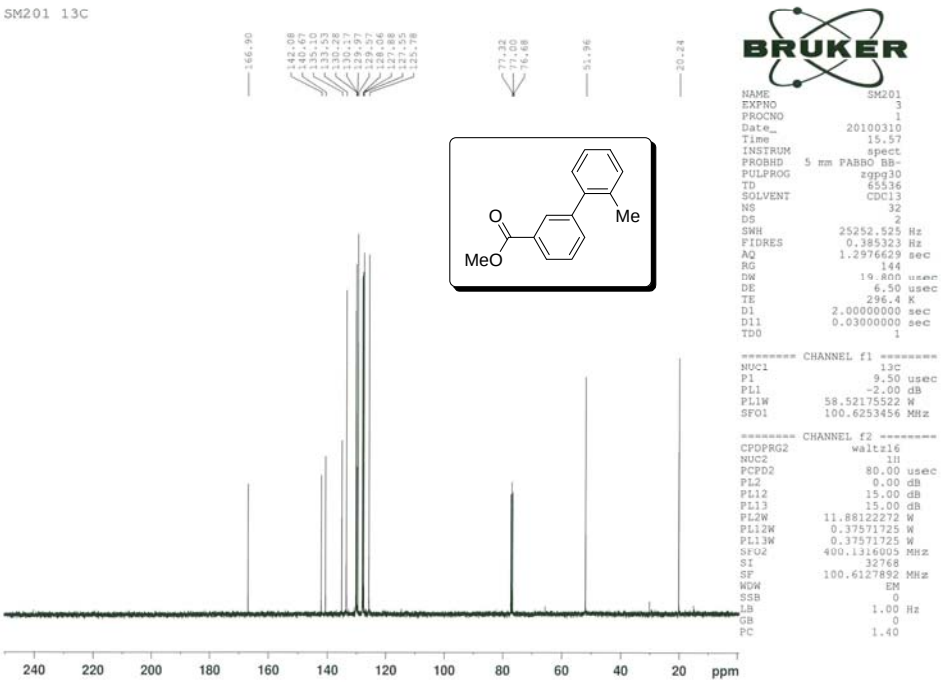
^{13}C NMR of entry 11



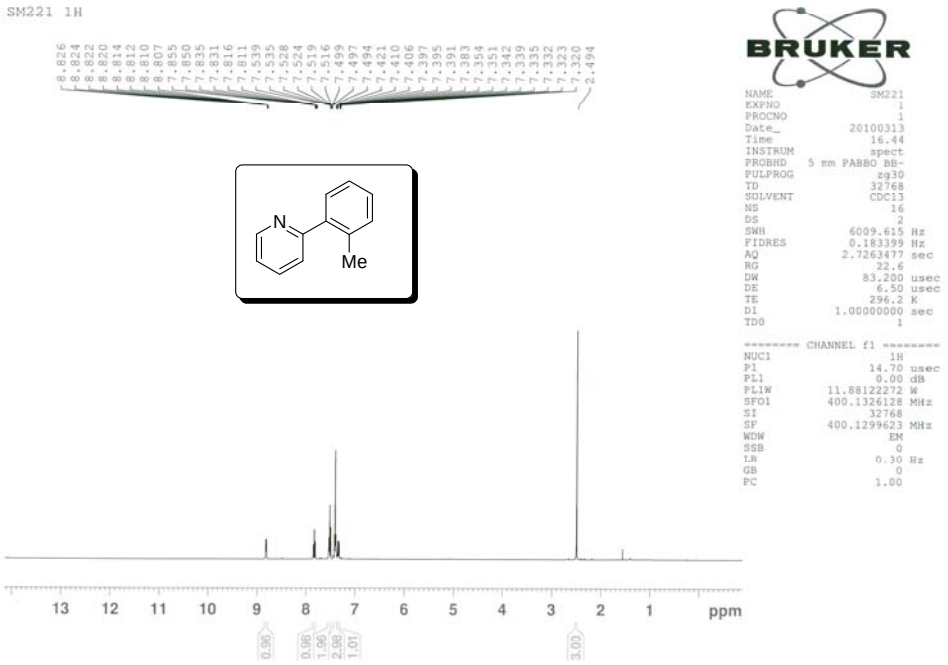
^{1}H NMR of entry 12



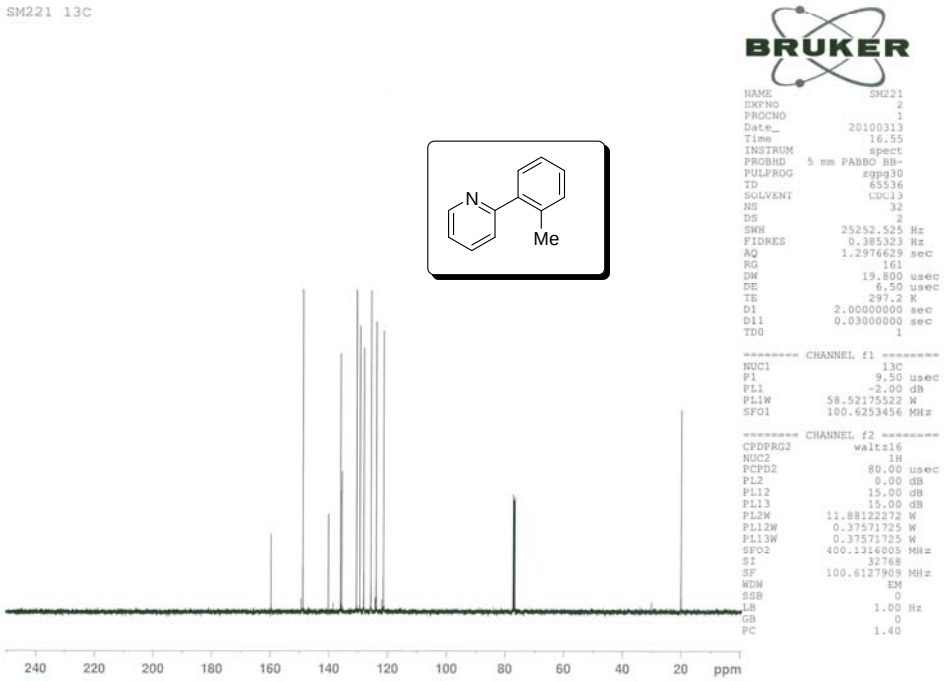
^{13}C NMR of entry 12



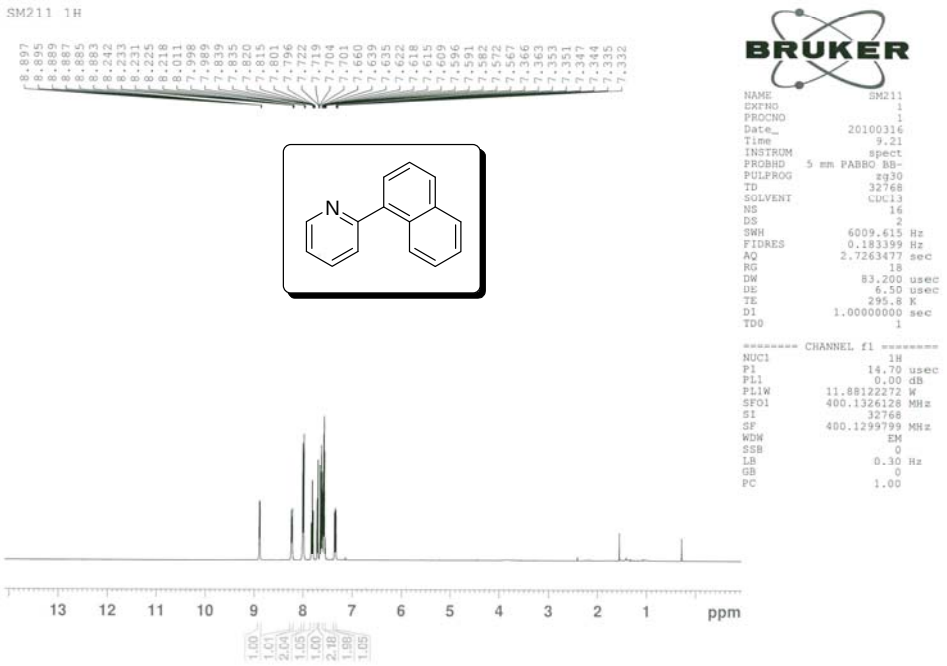
^{1}H NMR of entry 13



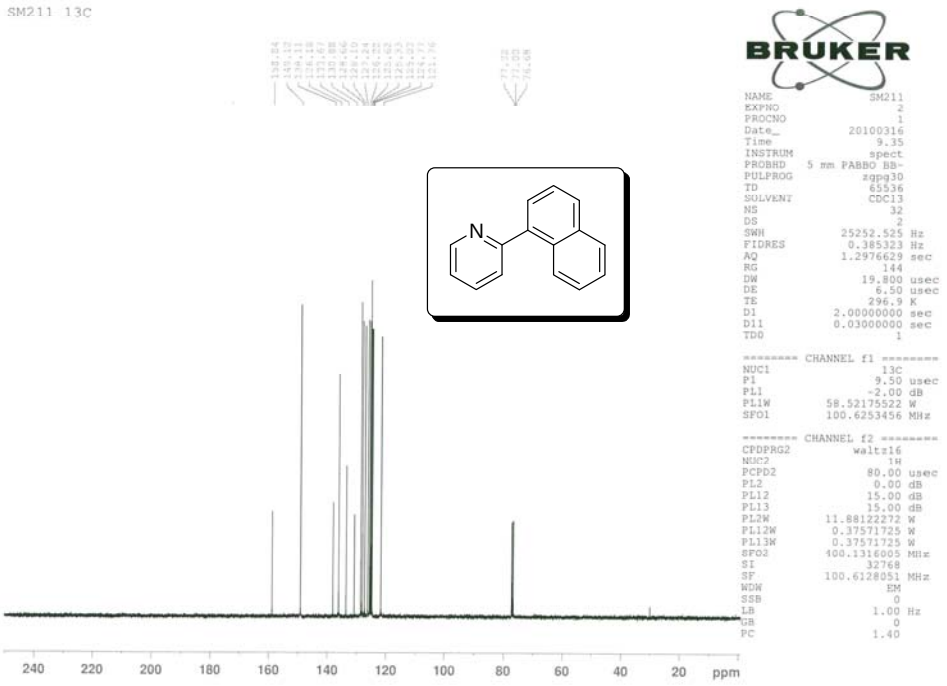
^{13}C NMR of entry 13



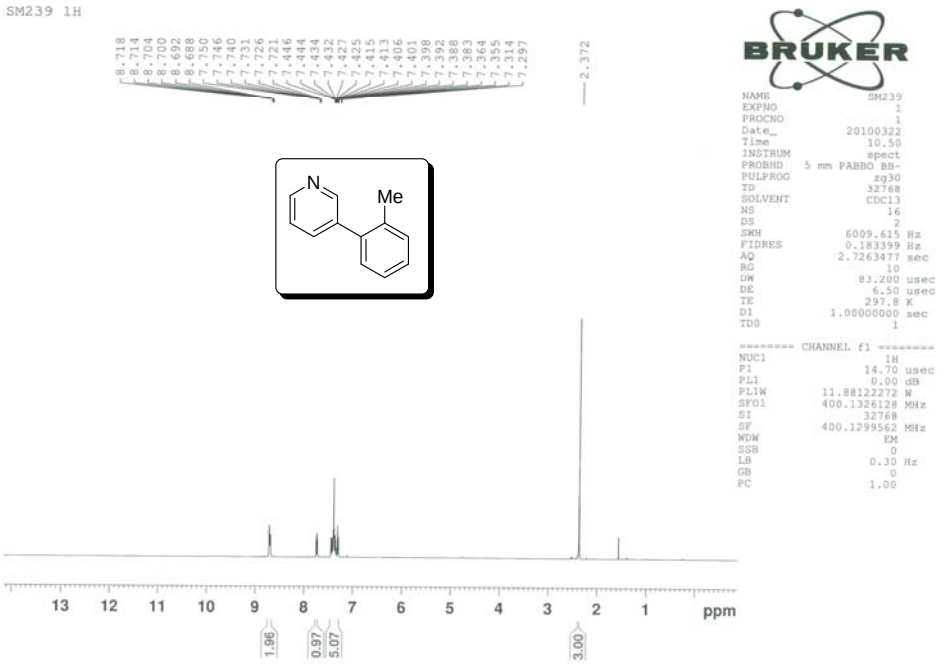
^{1}H NMR of entry 14



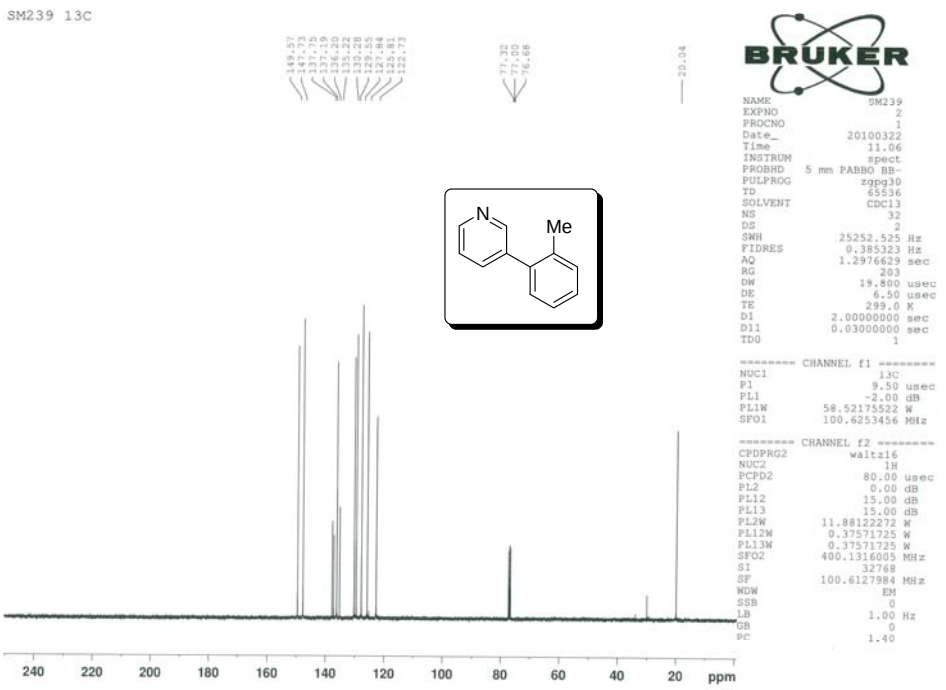
^{13}C NMR of entry 14



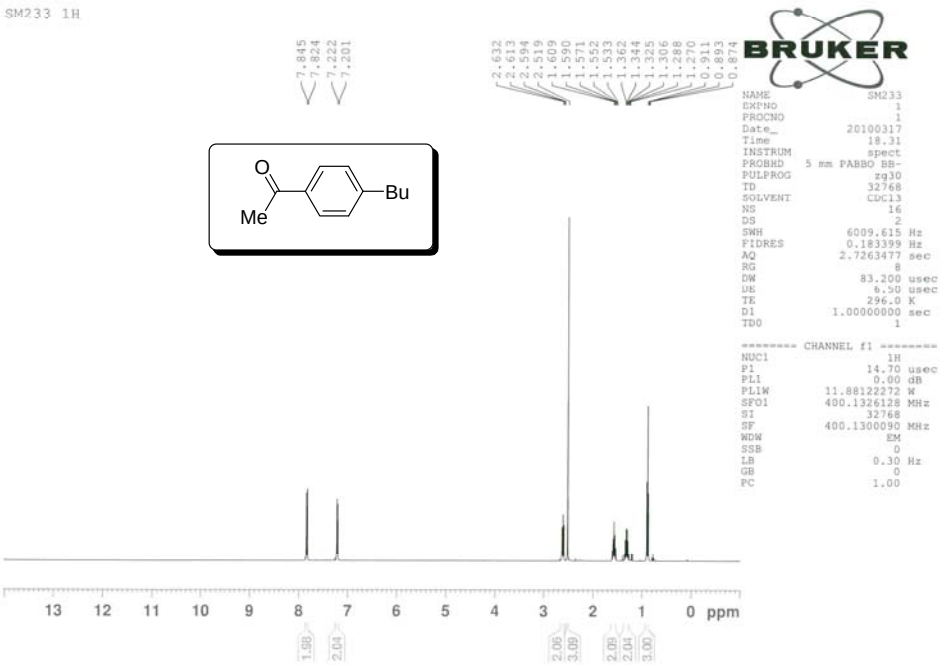
^{1}H NMR of entry 15



^{13}C NMR of entry 15



^{1}H NMR of entry 16



^{13}C NMR of entry 16